

Review Article

# Silver in dermatology - From ancient use to modern innovations

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## ABSTRACT

Silver, a metal known to mankind since early times, has gained the interest of researchers in recent times, exhibiting a growing trend in the use of silver in modern-day medicine. The biofilm-inhibiting and degrading effects of bioengineered silver nanoparticles have opened opportunities for future research in combating antimicrobial resistance. Silver has demonstrated a beneficial role in burns, wound healing, infections, papulosquamous disorders, and acne vulgaris. Silver has been used in cosmeceuticals, especially in deodorants, lipsticks, foundations, powders, and eyebrow pencils, owing to its antimicrobial and anti-inflammatory properties. The astringent and hemostatic properties of silver have also been utilized in skin care. Chronic exposure to silver causes its deposition in tissue referred to as 'argyria' which can be localized or generalized with a bluish-gray appearance due to the Tyndall effect. Allergic contact dermatitis has been reported due to contact with silver sulfadiazine, silver nitrate, and silver fulminate. Further research is needed to explore the promising avenues for silver in healthcare.

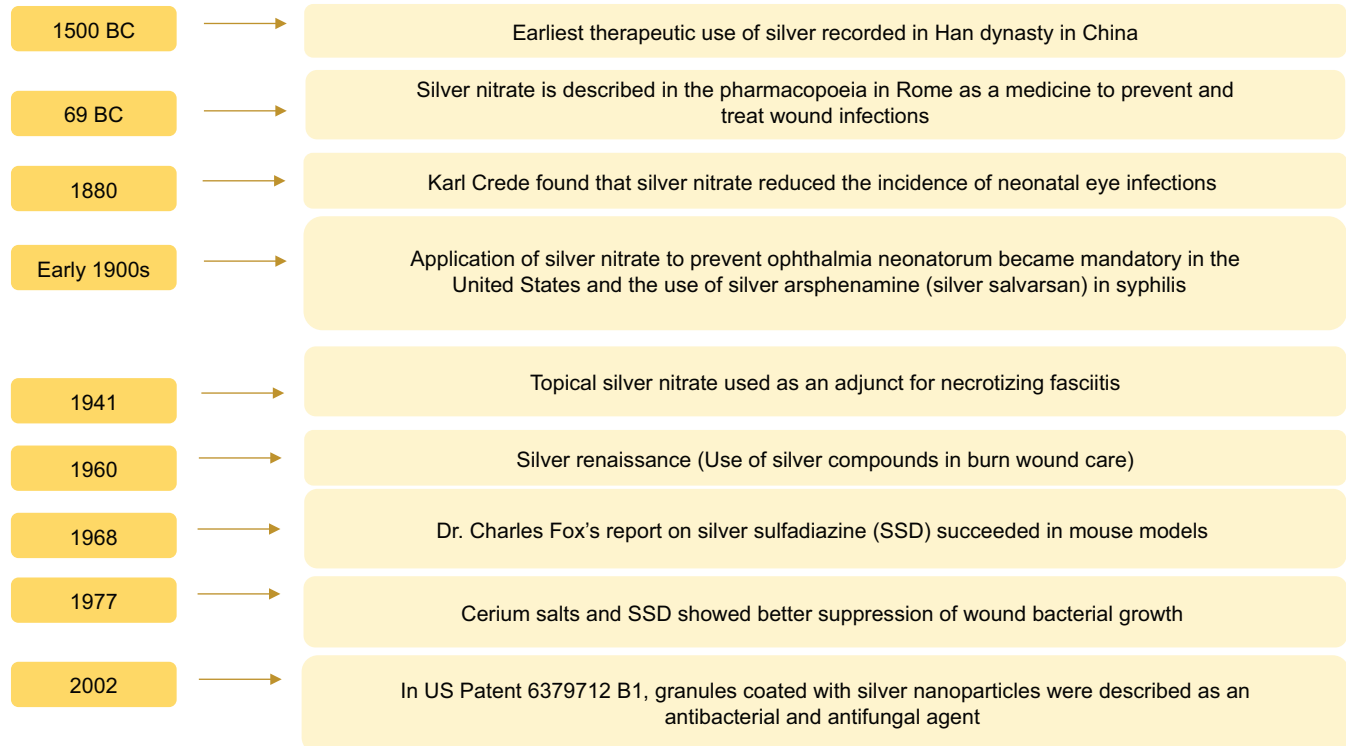
**Keywords:** Antimicrobial, Nanoparticle, Silver, Silver nanoparticles

## INTRODUCTION

Silver has a significant role in medicine owing to its antibacterial and antiseptic properties. Although known to mankind since early times, the metal has gained the interest of researchers in recent times with a growing trend in the use of silver in modern-day medicine.<sup>[1]</sup> The popular forms of silver include silver nitrate, colloidal silver, and silver sulfadiazine (SSD).<sup>[1]</sup> The use of silver nanoparticles (AgNPs) has been preferred in recent times due to their exceptional antimicrobial activity even at low concentrations. Moreover, the rise of antibacterial resistance has opened the way to explore AgNPs as effective antimicrobial agent.<sup>[2]</sup>

## HISTORY OF SILVER

The earliest use of silver was for safe water storage by the Greeks and Romans, while the first known therapeutic use of silver was in China in 1500 BC. The history of silver in medicine and dermatology is illustrated in Figure 1.<sup>[2,3]</sup>



**Figure 1:** Timeline of events in the history of silver in dermatology. BC: Before Christ.

## USES OF SILVER IN DERMATOLOGY

### Silver as an antimicrobial agent

The antimicrobial action of silver is directly proportional to the rate and the amount of silver being released, with the nature of the silver antimicrobial used being a pertinent factor in determining its efficacy.<sup>[4]</sup> The antimicrobial actions of silver are illustrated in Figure 2. A recent study has found synergistic activity of metal-metalloid-based antimicrobials (silver nitrate and potassium tellurite) with the advantage of combined bacteriostatic, bactericidal, and anti-biofilm activity.<sup>[5]</sup>

### Evolution of AgNPs and its antimicrobial role

With the development of nanotechnology, metals are modulated to their nano size, altering their inherent physical, chemical, and optical properties. AgNPs are nanomaterials with sizes ranging from 1 to 100 nm in all dimensions, with a higher area-to-volume ratio than silver.<sup>[6]</sup> AgNPs have gained popularity, given the existing and emerging antibiotic resistance to various antibiotics.<sup>[6]</sup> According to the United States Centers for Disease Control, biofilms, 10-1000 times more resistant to antimicrobials than planktonic bacteria, are responsible for 80% of human bacterial infections.<sup>[7]</sup> AgNPs are synthesized by physical, chemical, and biological methods. The AgNPs bioengineered by

microfabrication (*Saccharomyces cerevisiae*-derived AgNPs) and photofabrication (*Pimpinella anisum*-derived AgNPs) have shown significant antibacterial activity.<sup>[7,8]</sup> These bioengineered AgNPs have demonstrated antibiofilm activity against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella enterica*, and *Staphylococcus epidermis*.<sup>[7]</sup> The characteristic features of nanoparticles, such as their size, shape, surface charge, and surface chemistry, affect their biological and pharmacological properties.<sup>[9]</sup> AgNPs have also documented efficacy against vancomycin-resistant bacteria and offer a broad spectrum of antibiotic coverage.<sup>[10]</sup>

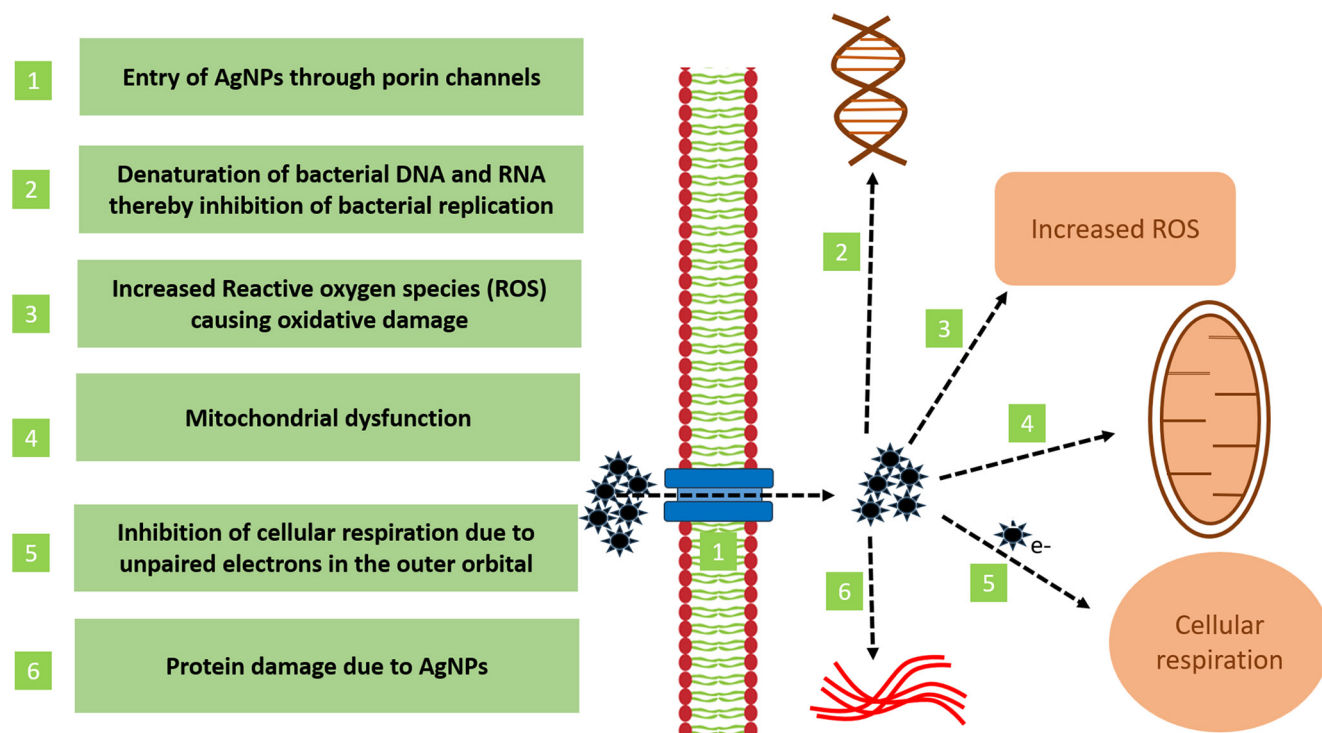
### Role of silver in specific infectious diseases

#### Uses of silver nitrate in viral infections

Silver nitrate is an effective caustic agent used to achieve hemostasis. Silver nitrate acts by causing coagulation of proteins, leading to tissue necrosis and eschar formation, eventually leading to thrombus formation and hemostasis.<sup>[11]</sup> The caustic property of silver nitrate has been used for various applications in dermatology, such as in warts and molluscum contagiosum.<sup>[11]</sup>

#### Warts

The self-limiting superficial penetration potential of silver nitrate makes it ideal for the treatment of warts, especially



**Figure 2:** Antimicrobial actions of silver. AgNPs: Silver nanoparticles, DNA: Deoxyribonucleic acid, RNA: Ribonucleic acid.

in patients with an increased risk of reduced tissue healing capacity. Silver nitrate (10%) is effective in the treatment of verruca vulgaris, causing 63.33% complete regression of lesions without significant side effects.<sup>[12]</sup> Verruca vulgaris treated with silver nitrate pencils has shown 43% complete resolution and 26% partial resolution.<sup>[13]</sup> The silver duct tape occlusion method has also been found to be effective in the management of plantar warts by creating a macerating and keratolytic environment, leading to stimulation of the immune response.<sup>[14]</sup> Silver nitrate application causes localized tissue irritation and immune reactions by the host against the virus, causing both biochemical and physical destruction.<sup>[15]</sup> Silver nitrate application to the periungual region causes gray-black staining and rarely gangrenous necrosis.<sup>[16]</sup>

Pox virus infections (Molluscum contagiosum [MC] and Monkeypox infections)

MC lesions responded well to 40% silver nitrate application, with 70% of lesions resolving in one application with a maximum of three applications needed for 97.7% resolution. Following application, the lesions become brown-black immediately, surrounded by an erythematous halo. Applying lignocaine jelly before the procedure prevents the erythematous flare, pruritus, and burning sensation.<sup>[17]</sup> A black crust forms before the MC lesion drops between days 10 and 14.<sup>[18]</sup> Silver nitrate paste has been tried successfully with 70% efficacy for MC to avoid unnecessary irritation

caused by dripping of solution formulation onto the normal skin.<sup>[17]</sup>

In a study by Rogers *et al.*, polysaccharide-coated AgNPs of size 10 nm and silver nitrate decreased monkeypox virus plaque formation by 60-79% and 29-40%, respectively.<sup>[19]</sup>

Herpes simplex virus (HSV) infection

A study by Pan *et al.*, showed that AgNPs inhibited HSV-1 by reducing plaque formation, viral progeny production, and genomic load. AgNPs also interfere with HSV-1 messenger RNA expression and protein synthesis, alter the shape of viral particles, affect the virus's entry, release, and cell-to-cell spread, and enhance the efficacy of acyclovir.<sup>[20]</sup> AgNPs in a concentration of 100 µg/mL have also been shown to inhibit HSV-2 replication *in vitro* completely.<sup>[21]</sup>

Human immunodeficiency virus (HIV)

AgNPs have demonstrated anti-HIV-1 activity by preventing CD4-dependent virion binding and fusion with a half-maximal inhibitory concentration between 0.44 and 0.91 mg/mL.<sup>[22]</sup> Silver ions, by themselves, exert lower efficiency in inhibiting HIV-1 infection *in vitro* than AgNPs. This is evident from a study that showed that the therapeutic index of silver salts such as silver nitrate and SSD in HIV-1 inhibition was 12 times lower than AgNPs.<sup>[22]</sup> It is also observed that the mutations in antiretroviral HIV strains

conferring resistance were not found to affect the efficacy of AgNPs.<sup>[22]</sup> However, the efficacy of AgNPs in HIV needs further confirmation with human studies since the majority of data are based on *in vitro* studies.<sup>[22]</sup>

#### Silver and antifungal effect

AgNPs produced by the bioreduction of aqueous Ag<sup>+</sup> ions by the leaf extract of *Solanum trilobatum* plant leaf have been found to have a higher inhibitory effect on *Pityrosporum ovale*. This effect has been proposed to enhance the efficacy of anti-dandruff shampoos. *S. trilobatum*-based AgNPs have also shown antifungal activity against *Candida albicans* and *Candida parapsilosis*.<sup>[23]</sup> Silver-zinc zeolite nanoparticles coated soft denture liners are beneficial in the prevention of oral candidiasis.<sup>[24]</sup> AgNPs have demonstrated antifungal activity against *Microsporum canis*, *Trichophyton mentagrophytes*, and *Microsporum gypseum* by creating pores in cell walls and plasma membranes and also against invasive mycosis like mucormycosis.<sup>[25,26]</sup> Recently, antifungal creams such as luliconazole and ketoconazole have been combined with AgNPs to combat superficial mycoses.<sup>[27,28]</sup> The various mechanisms by which AgNPs exhibit their antifungal effect are illustrated in Figure 3.<sup>[29]</sup>

#### Silver in parasitic infections

AgNP impairs the glycoprotein present on the surface of the parasite and can inhibit the proliferation of promastigotes, as demonstrated by Allahverdiyev *et al.*, in *Leishmania tropica*. It was further studied that in the presence of increased ultraviolet light, AgNP further hampers amastigote endurance in the host cell.<sup>[30]</sup> Inhibitory action against *Leishmania amazonensis* has also been studied.<sup>[31]</sup>

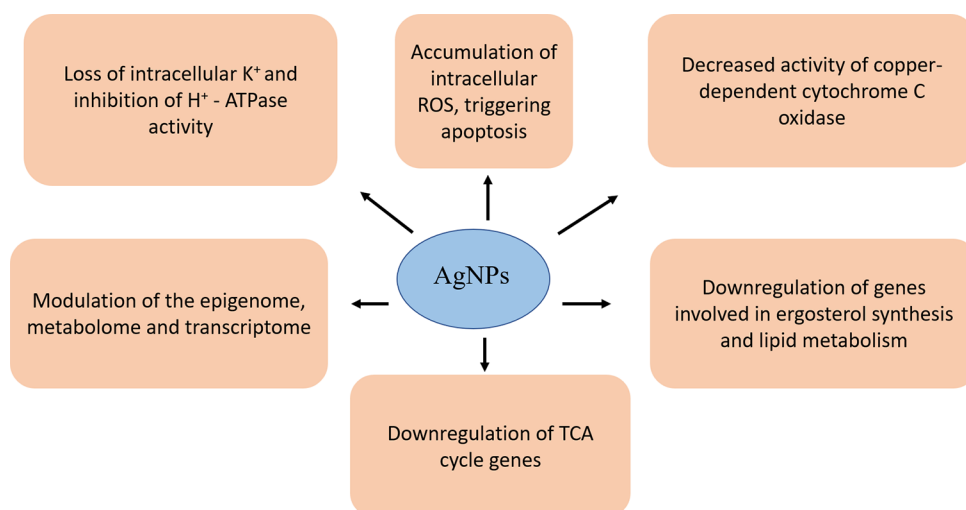
#### Antimicrobial resistance to silver

Rampant use of silver-containing compounds has led to documented resistance of Ag to a few bacteria and fungi, especially in burn wards.<sup>[32]</sup> Significant mechanisms of resistance documented are due to the plasmid sil operon, copper-silver efflux systems, silver cation efflux proteins, and biofilm formation. The biofilm formation has been attributed to Bap1 and RbmA, and the binding of Ag<sup>+</sup> ions with the negatively charged extracellular polymeric substances. Cross-resistance in bacteria (*Serratia marcescens*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Enterococcus durans*, and *Enterococcus gallinarum*) has been noted between silver and other heavy metals such as mercury, arsenic, copper, tellurite, and zinc.<sup>[33]</sup>

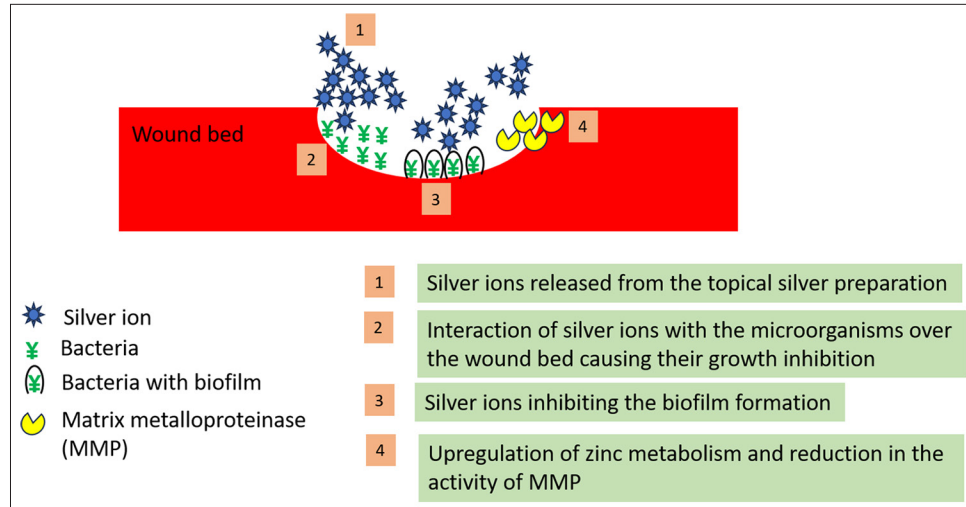
#### Silver in burns and wound healing

Silver compounds have been exploited for their noteworthy role in the management of burns. The gold standard silver agent in the management of burns is SSD.<sup>[34]</sup> Silver nitrate (0.5%) is considered the standard and popular silver salt solution for burn wound therapy. On the contrary, the reduction of nitrate to nitrite can lead to oxidative cell damage, impairing re-epithelialization.<sup>[34]</sup>

The benefits of silver in wound healing can be attributed to various reasons, such as broad-spectrum antimicrobial activity, reduction in the activity of matrix metalloproteinase, combating biofilm formation, and its anti-inflammatory properties.<sup>[35,36]</sup> An ideal silver dressing maintains a sustained, therapeutic silver ion concentration (>30 ppm) while not causing local or systemic toxicity (≤60 ppm). The role of silver in wound healing is illustrated in Figure 4.



**Figure 3:** Mechanism of antifungal action of silver nanoparticles. AgNPs: Silver nanoparticles, ROS: Reactive oxygen species, ATPase: Adenosine triphosphatase, K<sup>+</sup>: Potassium ion, H<sup>+</sup>: Hydrogen ion, C oxidase: Cytochrome C oxidase, TCA: Tricarboxylic acid.



**Figure 4:** Role of silver in wound healing.

The various forms of silver dressings used in wound care include SSD, silver-coated nylon, silver-coated polyethylene, silver-coated foam, silver-coated silicone, silver-coated cellulose hydrofiber, and silver-coated polyurethane (PU) sponge.<sup>[35]</sup> Silver-coated PU negative pressure wound therapy (NPWT) combines the benefit of NPWT and delivers an optimal concentration of silver that is below the toxic threshold to fibroblasts and keratinocytes.<sup>[35]</sup> The advantages of silver-containing dressings include less frequent change of dressing, reduced pain levels, and accelerated wound healing in contaminated wounds. Silver has no beneficial role in non-infected clean wounds as it can delay epithelialization.<sup>[35]</sup>

Dynamic reversible hydrogels have demonstrated a significant application in wound dressing. The use of SSD as a catalyst for the construction of hyaluronic acid-based hydrogels has enabled hydrogels to possess concurrent dynamics, stability, and antimicrobial properties.<sup>[37]</sup> Silver in dressings can be either in ionic form or metallic form (extremely small crystals or nanocrystals). The metallic silver needs to react with substances in the wound bed to form soluble salts such as silver nitrate, silver chloride, or silver oxide, releasing free silver ions.<sup>[36]</sup>

AgNP-loaded collagen chitosan dressing exerted significant biological effects on wound healing by regulation of growth and inflammatory factors (vascular endothelial growth factor [VEGF], basic fibroblast growth factor, transforming growth factor-beta 1, interleukin [IL]-1 beta, and epidermal growth factor-like domain 7).<sup>[38]</sup>

### Silver in graft procedures

NPWT combined with AgNP sheets has shown better results in patients undergoing graft procedures in terms

of better graft integration and decreased levels of systemic inflammatory markers.<sup>[39]</sup>

### Silver as an astringent

Silver nitrate is used as an astringent in concentrations of 0.1-0.5% by drawing water out of the cells, causing dryness of exudative lesions. Hence, it is used in the management of leg ulcers and burns. Higher concentrations of silver nitrate are found to induce pain.<sup>[40]</sup>

### Silver in hyperhidrosis and bromhidrosis

PU sheets, modified using hydrophilic polymers and coated with SSD, are used as cushion insoles in patients with plantar hyperhidrosis. Perspiration leads to the swelling of hydrophilic polymers on the PU surface, causing SSD release, which has bactericidal properties. Hence, silver prevents bad odor in bromhidrosis and bacterial infections in plantar hyperhidrosis.<sup>[41]</sup> In a randomized controlled trial by Celleno *et al.*, an antiperspirant product based on silver citrate, aluminum hydrochloride, and agaricine showed beneficial antiperspirant and anti-bacterial activity with the added advantage of not staining the clothes.<sup>[42]</sup>

### Silver as a hemostatic agent

Silver nitrate is an inexpensive, readily available topical hemostatic agent effective in concentrations of 10% applied with light pressure over the bleeding site after application.<sup>[43]</sup> Interaction of silver ions with proteins causes denaturation and precipitation of proteins and obstruction of small vessels. Silver nitrate application causes the formation of a thin eschar which prevents the formation of deep tissue necrosis.<sup>[44]</sup> Side effects of topical silver nitrate application include a burning



sensation and temporary black discoloration.<sup>[44]</sup> However, application over large areas can cause permanent black discoloration due to silver particle impregnation. Inadvertent application of silver nitrate in large amounts can be neutralized by saline application.<sup>[43]</sup>

### Silver in papulosquamous disorders

#### Silver in psoriasis

AgNPs complexed with *Cornus mas* modulate inflammation in psoriasis both at the molecular and cellular levels.<sup>[45]</sup> They have been found to reduce CD-68 positive macrophages, tumor necrosis factor (TNF), and IL-12 production in the psoriatic plaques, representing a novel “green” technology in modern psoriasis therapy. AgNPs resulted in reduced erythema, scaling, and plaque thickness with good long-term tolerability, devoid of treatment-related side effects.<sup>[45]</sup>

#### Bioengineered AgNPs coated textiles in atopic dermatitis

A combination of micro silver and nano lipid carriers (sNLC and NLC) has been used in the management of atopic dermatitis. The positive silver ions adsorb onto the negatively charged NLC to form sNLC, which adheres to the skin and bacterial surfaces, causing effective killing of the bacteria.<sup>[46]</sup> Bioengineered silver-based nanomaterial coatings have been used in cotton textiles, causing effective reduction of *S. aureus* colonization in patients with atopic dermatitis. The effect of AgNPs coated silver textiles starts 2 days after application and lasts for 1 week after removal of clothing.<sup>[47]</sup>

### Silver in autoimmune bullous disorders

Topical nano colloidal silver is effective in the management of hard-to-heal ulcers of pemphigus vulgaris with a significant positive effect on the ulcer area and exudate.<sup>[48]</sup> Physiotulle silver dressings containing silver used in erosions of pemphigus vulgaris resulted in a significant reduction of pain score, reduced length of hospital stay, and reduced frequency of change of dressings.<sup>[49]</sup>

### Silver in onychocryptosis

High-strength silver nitrate is beneficial in the management of hypergranulation tissue, complicating ingrown toenails in concentrations of 40%, 75%, and 90% through applicator sticks.<sup>[50]</sup>

### Silver in umbilical granuloma

Umbilical granuloma, which presents with a pinkish to skin-colored granulomatous tissue, is the most documented

umbilical abnormality in neonates. Careful application of silver nitrate 20% has been used once weekly over the lesion till resolution while protecting the surrounding area with petroleum jelly. Considering high rates of caustic burns and post-inflammatory pigmentation, other treatment modalities, such as the usage of common salt, electrocautery, cryotherapy, and topical steroids, are preferred.<sup>[51]</sup>

### Silver in acne vulgaris

Acne vulgaris, due to its chronic and relapsing nature, demands long-term antibiotic use, resulting in antibiotic resistance demanding the use of alternative treatment options. With the use of AgNP gel on the rising trend, the combination of AgNP gel and 2.5% benzoyl peroxide is effective in both moderate inflammatory and non-inflammatory acne lesions.<sup>[52]</sup> A combination of AgNPs and extracts of *Azadirachta indica* (neem) leaves and *Curcuma caesia* rhizome has demonstrated good antibacterial activity against *Propionibacterium acnes* with a sustained drug release.<sup>[53,54]</sup>

### Silver socks in epidermolysis bullosa

Silver-fibered cotton socks and silver vinyl insole material can be used for foot care in epidermolysis bullosa which has the advantages of reducing friction and heat, conducting heat away from the skin, and additional antibacterial action.<sup>[55]</sup>

### Silver in cosmeceuticals

With the growing trend in the use of skincare and cosmetic products, consumers prefer safer products with long-term efficacy. This has led to the use of the term “cosmeceutical,” implying the overlap of cosmetics and pharmaceuticals. The cosmeceutical industry has integrated nanotechnology in the form of AgNPs in various products such as moisturizers, sunscreens, lipsticks, face cleansers, whitening creams, deodorants, toothpaste, and anti-aging products.<sup>[56]</sup> The combination of silver and gold nanoparticles to produce yellow-red pigment has been utilized in the production of various cosmetic products such as lipsticks, foundations, powders, and eyebrow pencils.<sup>[54]</sup>

Preference for silver as a nanoparticle in cosmeceuticals is attributed to its antimicrobial and anti-inflammatory properties.<sup>[56]</sup> The anti-inflammatory effects are due to disruption of the VEGF pathway, decrease in TNF-alpha and IL-6, inhibitory effect on nuclear factor-κB signaling, and inhibition of prostaglandin and cyclooxygenase synthesis.<sup>[56]</sup> Silver zeolite has been used as a deodorant in the axilla due to its strong and long-lasting bactericidal ability.<sup>[57]</sup> The uses of silver in dermatology, venereology, and leprosy have been summarized in Table 1.

**Table 1:** Uses of silver in dermatology, venereology, and leprosy.

S. No.	Uses	Form of silver
1.	Antibacterial activity	
	Broad spectrum covering <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Bacillus subtilis</i> , <i>Pseudomonas aeruginosa</i> , and <i>Salmonella Typhi</i>	Silver nitrate, SSD, silver zeolite, silver-zinc zeolite nanoparticles, silver-tellurite, AgNPs
	Leprosy	Gold-silver nanoparticle combination
	Syphilis	Silver arsphenamine
	Antiviral activity	
	Warts	Silver nitrate
	Molluscum contagiosum	Silver nitrate
	HSV infection	AgNPs
	HIV infection	AgNPs
	Antifungal activity	
	Candidiasis ( <i>Candida albicans</i> , <i>Candida parasilosis</i> )	AgNPs
	Pityrosporum folliculitis ( <i>Pityrosporum ovale</i> )	
	Dermatophytosis ( <i>Trichophyton mentagrophytes</i> , <i>Microsporum gypseum</i> )	
	Mucormycosis	
	Parasitic infections	
	Leishmaniasis	AgNPs
2.	Wound healing including graft procedures	SSD, silver-coated nylon, silver-coated polyethylene, silver-coated foam, silver-coated silicone, silver-coated cellulose hydrofiber, and silver-coated polyurethane sponge
3.	As an astringent	Silver nitrate
4.	As a hemostatic agent	Silver nitrate
5.	Papulosquamous disorders	
	Psoriasis	AgNPs
	Atopic dermatitis	Microsilver and nanolipid carrier Silver-coated cotton textiles
6.	Acne vulgaris	AgNPs
7.	Autoimmune bullous disorders	Nano colloidal silver
8.	Miscellaneous	
	Umbilical granuloma	Silver nitrate
	Epidermolysis bullosa	Silver-fibred cotton socks
	Onychocryptosis	Silver nitrate
	Use in cosmeceuticals	AgNPs and silver zeolite

AgNPs: Silver nanoparticles, SSD: Silver sulfadiazine, HSV: Herpes simplex virus, HIV: Human immunodeficiency virus

### Use of silver-coated instruments in dermatology

The antimicrobial properties of silver have been highly valued in varied medical applications through the silver coating of instruments. Ready-to-use medical instruments with instant antimicrobial effects have been devised, which activate bioactive silver coating upon package opening.<sup>[1]</sup> Invasive surgical tools, including medical needles, are coated with AgNPs with a particle diameter of 0.1-300 nm and silver

concentration of 0.01-20% to prevent infection and provide pain relief. It was found that a silver concentration of <0.01% shows negligible antimicrobial effect, and more than 20% reduces the needle strength.<sup>[1]</sup>

### Silver stains

Silver staining involves utilizing silver to selectively modify the appearance of a specific target in the microscopy of

histological sections. The uses of silver stains in dermatology are mentioned in Table 2.<sup>[58-60]</sup>

### Silver in Raman spectroscopy

Raman spectroscopy has been used recently to diagnose skin diseases, especially skin tumors such as basal cell carcinoma and melanoma, based on autofluorescence. AgNPs with unique optical properties of strong absorption and scattering of light have made them useful in surface-enhanced Raman spectroscopy.<sup>[8]</sup>

## SIDE EFFECTS OF SILVER

### Argyria

The term “argyria” derived from the Greek word *argyros*, meaning silver, was coined by Fuchs in 1840. It is an uncommon benign condition characterized by chronic exposure and the deposition of silver in the tissue.<sup>[61,62]</sup> Argyria can be localized or generalized based on the mode and quantity of silver absorbed.<sup>[62]</sup> The commonly characterized forms of localized argyrias are (i) cutaneous, (ii) oral cavity, and (iii) ocular. A few unusual localized argyrias are penis, vagina, urinary tract, nasal mucosa, and trachea.<sup>[61,62]</sup>

Generalized argyrias occur due to systemic absorption of silver that gets widely deposited in the skin, nails, eyes, and mucous membranes.<sup>[61]</sup> As alternative medicine gains popularity, the availability of silver-containing solutions increases, consequently raising the incidence of argyria. This trend is particularly noticeable in Asia, where there is a growing number of case reports documenting instances of

argyria.<sup>[63]</sup> Exceeding the daily oral exposure of 5 µg/kg/day of silver exposes the patients to risks of skin discoloration.<sup>[64]</sup>

Apart from cutaneous deposition of silver, systemic side effects such as renal toxicity, leukopenia, and cytotoxicity have also been reported, especially through SSD dressings in burns involving >40% of body surface area.<sup>[34]</sup>

Localized argyrias occur due to the impregnation of silver confined to the site of direct contact, especially in professions such as silversmithing and industries involving photography, soldering, batteries, and mirrors. Dental procedures, including those involving amalgam tattooing, as well as the use of silver jewelry such as earrings and nasal piercings, have also been linked to localized argyria.<sup>[65]</sup> The presence of the Tyndall effect causes the brown colloidal silver particles located in the dermis to give off a bluish-gray appearance when observed through the skin.<sup>[66]</sup> The differential diagnoses of argyria are mentioned in Table 3.

Histologically, yellow-brown colored collagen bundles resembling pseudo-ochronosis have been described occasionally.<sup>[61]</sup> Management options include sunscreens, 1064 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser, 755 nm alexandrite laser, and low-fluence Q-switched Nd:YAG laser and avoidance of offending silver-containing agents.<sup>[63,67]</sup>

### Silver as an allergen

Most of the cases of allergic contact dermatitis (ACD) to silver seem to be related to occupation, such as jewelers, photographers, and silver miners.<sup>[68]</sup> ACD has been reported to be silver sulfadiazine, silver nitrate, or silver fulminate.<sup>[69]</sup> The side effects of topical silver preparations include stinging,

**Table 2:** Application of silver stains in dermatology.

Category	Stain (s)	Structures demonstrated
Argentaffin-silver reduction	Fontana-Masson	Argentaffin tumors, melanomas, and some carcinoid tumors
Argyrophil-absorption		
Acidic	Warthin-Starry, Dieterle, Steiner and Steiner	Spirochetes and other bacteria
	Acid melanin stain	Melanomas
Basic	Grimelius	Neuroendocrine secretory granules
Neutral	AgNOR stain	Nucleolar organizer region
Argyrophil-impregnation		
Type I	Bodian, Bielschowsky	Neurites
Type II	Golgi	Neurites
Argyrophil-oxidation-reduction	Grocott's Modified Gomori	Fungi
	Methenamine silver stain	
	Jones stain	Basement membranes
	Reticulum stain	Reticular fibers



**Table 3:** Clinical differential diagnoses of argyria.

S. No.	Differential diagnosis	S. No.	Differential diagnosis
1.	Metals deposition <ul style="list-style-type: none"> <li>• Gold</li> <li>• Lead</li> <li>• Arsenic</li> <li>• Mercury</li> <li>• Bismuth</li> </ul>	4.	Nutritional deficiencies <ul style="list-style-type: none"> <li>• Vitamin B3</li> <li>• Folic acid</li> <li>• Vitamin B12</li> </ul>
2.	Drug deposition <ul style="list-style-type: none"> <li>• Amiodarone</li> <li>• Antimalarial</li> <li>• Clofazimine</li> <li>• Minocycline</li> <li>• Methacycline</li> <li>• Tetracycline</li> <li>• Phenothiazines</li> <li>• Phenytoin</li> </ul>	5.	Endocrine disorders <ul style="list-style-type: none"> <li>• Addison's disease</li> <li>• Acromegaly</li> <li>• Hypothyroid condition</li> </ul>
3.	Metabolic conditions <ul style="list-style-type: none"> <li>• Addison's disease</li> <li>• Cyanosis</li> <li>• Hemochromatosis</li> <li>• Methemoglobinemia</li> <li>• Ochronosis</li> <li>• Wilson's disease</li> </ul>	6.	Dermatological conditions <ul style="list-style-type: none"> <li>• Lichen planus pigmentosus</li> <li>• Erythema dyschromicum perstans</li> </ul>

pain, redness, chemical burns, and post-inflammatory pigmentation.<sup>[70]</sup> The widespread erythema with irritant contact dermatitis is seen especially in atopic individuals and in clustered lesions over the intertriginous areas.<sup>[17]</sup>

## CONCLUSION

Silver is a historic metal with diverse applications in dermatology and various fields of medicine. Silver has demonstrated its efficacy and versatility, from infection control and wound healing to its advancing role in skincare. The antibacterial and biofilm inhibitory effects of silver and AgNPs have a greater role to play in the future, especially in this era of growing antimicrobial resistance. Further research is needed to explore the possible promising avenues for silver in healthcare.

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