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Review article

Bridging therapeutic gaps in upper respiratory tract infections: the potential of silver nanoparticles in modern topical formulations

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ABSTRACT

Upper respiratory tract infections (URTIs) remain a significant health issue, with current treatments limited to symptom management and antibiotics for bacterial cases. No approved topical treatments exist for prevention and treatment across pathogens. Silver nanoparticles (AgNPs) are promising due to their broad-spectrum antimicrobial properties, disrupting microbial cells and essential functions. This review evaluates the efficacy, safety, and potential of AgNP-based topical treatments like nasal sprays and microemulsions, which offer localized action, reduced side effects, and improved adherence. While nasal sprays provide convenience, microemulsions enhance bioavailability through sustained release. However, large-scale trials are needed to validate their safety and effectiveness. Unlike existing reviews, this work focuses specifically on topical applications, comparing different delivery systems and highlighting their respective advantages. The review outlines key pharmacological insights and proposes research directions for developing targeted, effective URTI therapies.

Keywords: silver nanoparticles, upper respiratory tract infections, antimicrobial efficacy, nasal microemulsions, topical drug delivery

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Introduction

Upper respiratory tract infections: causes, treatment, and gaps

Upper respiratory tract infections (URTIs) remain prevalent health concerns globally, caused by a wide range of microorganisms, including viruses, bacteria, and fungi, which can lead to conditions such as the common cold, viral pharyngitis, bacterial pharyngitis, and acute bacterial rhinosinusitis.[1,2] In 2021, there were 12.8 billion global episodes of URTIs, with the highest incidence in children under 5 years, highlighting the widespread and persistent nature of these infections. Despite a decline in incidence rates since 1990, URTIs remain the leading cause of acute illness globally, imposing significant health, economic, and productivity burdens.[2] These infections significantly impact patients' quality of life, with the extent of the effect depending on the severity of the infection and potential complications.[3] Key management strategies focus on eradicating the causative pathogens, alleviating symptoms, and preventing recurrence or reinfection. Current guidelines advocate the use of antibiotics for bacterial or fungal infections, based on the type or suspected pathogen.[4] However, antiviral therapy is not recommended for the common cold. If managed inadequately, the common cold can progress to bacterial infections, such as acute bacterial rhinosinusitis.[5] Notably, there are no approved topical agents available for both the treatment and prevention of these infections. While some studies have investigated the effectiveness of certain substances, they have not been extensively studied in large populations or approved for clinical use. Table 1 outlines evidence regarding common URTIs, including their causes, primary treatments, and topical products evaluated in human clinical trials.[6-8] Table 1 details the etiologies, primary therapeutic strategies, and topical agents assessed in clinical studies for prevalent URTIs, such as the common cold, acute bacterial rhinosinusitis, and pharyngitis.[9] Current treatment modalities are primarily aimed at symptom management, with antibiotics being the mainstay for bacterial infections.[10]

Current therapies for URTIs are hindered by pathogen-specific treatments; overreliance on antibiotics; limited approved topical agents; and inadequate focus on inflammation. Poor patient adherence; systemic side effects; and insufficient prophylactic measures further reduce their effectiveness. Despite advances in URTI management, a substantial gap remains in the development and approval of effective topical treatments for both prevention and therapy. While nasal and throat sprays, such as saline, xylitol, and antiseptic solutions, have been evaluated,[11] none have gained widespread clinical acceptance or formal approval. A key limitation is the lack of robust clinical evidence supporting the efficacy of these topical therapies,[12] highlighting the need for innovative, broad-spectrum approaches like silver nanoparticle-based treatments.

Many existing studies are constrained by small sample sizes and insufficient statistical power, limiting their ability to provide definitive conclusions on the therapeutic or preventive efficacy of these agents. As a result, treatment remains largely supportive, with no approved topical interventions that effectively target both the pathogens and the associated inflammatory responses. Addressing these gaps necessitates the exploration of novel topical therapies.[13] Future research should prioritize large-scale, rigorously designed clinical trials to assess the efficacy and safety of topical agents with antiviral, antibacterial, and anti-inflammatory properties. Furthermore, the development of prophylactic topical treatments,[14] such as antiviral nasal sprays or throat rinses, should be considered, particularly for high-risk populations. These products could complement existing therapies, potentially reducing the incidence and recurrence of URTIs[15,16] while offering a more targeted

approach to both treatment and prevention. Expanding research in this field may ultimately yield more comprehensive and effective strategies for managing these prevalent and impactful infections.

Pharmacological history and antimicrobial applications of silver nanoparticles

A comprehensive review of the literature highlights the significant promise of metal nanoparticles, particularly silver, in preventing and treating URTIs. Historically, silver's antibacterial properties have been recognized across cultures and eras. Ancient uses include Persian military campaigns where silver was used to transport clean drinking water[17] and Avicenna's use of silver filings in 980 C.E. for blood purification and addressing ailments like heart palpitations and bad breath.[18] In the 18th and 19th centuries, colloidal silver was employed as a wound antiseptic, and silver nitrate was used for burning treatments and preventing gonorrheal ophthalmia in newborns.[17, 19] Its ingestion for stomach ulcer treatment persisted into the 1940s, and its use in coins and cutlery further demonstrated its inherent antimicrobial properties.[20] Today, silver's antimicrobial effectiveness is applied extensively. It is used in textiles and sprays to neutralize odor-causing bacteria[20-22] and incorporated into cosmetics for its antimicrobial benefits.[23,24] Silver sulfadiazine, an FDA-approved topical antibiotic, remains a standard in burn wound management due to its broad-spectrum coverage.[25,26] Medical and dental instruments, along with implants, leverage silver coatings to prevent infections.[17,27] Currently, over 300 clinical trials are exploring silver-containing compounds for a wide range of therapeutic and preventive applications.[28] While most applications involve topical or surface treatments, silver's proven efficacy and safety profile positions it as a strong candidate for future AgNP-based treatment and prevention of URTIs.

Silver nanoparticles

Nanoparticles are characterized as particulate matter with at least one dimension measuring less than 100 nm.[29] They exhibit a variety of shapes, including spheres, rods, cubes, tubes, and complex structures. Among the various nanoparticles with notable bioactivity, AgNPs are particularly distinguished for their extensive antimicrobial properties.[30] They have demonstrated effectiveness against a wide range of microorganisms, including bacteria, fungi, and viruses.[31] Recent years have seen a significant increase in dedicated research focused on the potential applications of AgNPs, indicating a promising trajectory in scientific exploration. In addition to their established antimicrobial efficacy, AgNPs have revealed versatility across multiple scientific domains. These applications include ground-breaking advancements in wound healing, innovative approaches to retinal therapies, and the development of pharmaceutical interventions, particularly in anticancer and antioxidant therapies.[32]

Characterization of silver nanoparticles

The characterization of AgNPs relies on a range of advanced measurement techniques, each contributing valuable information about the nanoparticles' properties. These techniques include UV–visible spectroscopy; Fourier-transform infrared (FTIR) spectroscopy; X-ray diffraction (XRD); X-ray photoelectron spectroscopy (XPS); dynamic light scattering (DLS); scanning electron microscopy (SEM); energy-dispersive X-ray spectroscopy (EDX/EDS); atomic force microscopy (AFM); transmission electron microscopy (TEM); particle size analysis (PSA); selected area electron diffraction (SAED) patterns; thermal gravimetric analysis (TGA); and nanoparticle tracking analysis (NTA). Together, they provide detailed insights into key characteristics, such as particle size, shape, crystallinity, zeta potential, surface area, porosity, solubility, aggregation behavior, adsorption capabilities, and fractal

dimensions.[33-35] A crucial step in confirming the successful synthesis of AgNPs is the visual detection of a brownish hue, commonly observed when silver salts react with plant extracts. This distinct color change results from surface plasmon resonance (SPR), a phenomenon caused by the collective oscillation of conduction-band electrons in response to incident light waves. The resonance effect is typically detected through UV–visible spectrophotometry, where SPR peaks appear within the 400–500 nm wavelength range, confirming the formation of AgNPs.[36-37] These characterization methods ensure a thorough understanding of the nanoparticles, which is essential for optimizing their performance in various applications. Table 2 shows common techniques for the characterization of nanoparticles.

Table 1 Causes, primary treatments, and topical products evaluated for common upper respiratory tract infections.

Condition	Causes	Primary treatments	Topical products evaluated in human clinical studies
Common cold	Viruses (e.g., rhinoviruses, coronaviruses)	Symptomatic relief (e.g., decongestants, antihistamines, analgesics)	No approved topical products: studies on nasal sprays (e.g., saline, xylitol) have been conducted but not widely accepted or approved
Acute bacterial rhinosinusitis	Bacteria (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*)	Antibiotics (e.g., amoxicillin-clavulanate), symptomatic treatment (nasal decongestants, saline nasal irrigation)	No approved topical treatments: intranasal corticosteroids have been studied but are not standard treatments for infection
Pharyngitis	Viruses (viral pharyngitis) or bacteria (*Streptococcus pyogenes* for bacterial pharyngitis)	Viral: Symptomatic relief (e.g., analgesics, lozenges); Bacterial: Antibiotics (e.g., penicillin V, amoxicillin)	No approved topical products: some studies on throat sprays with antiseptics (e.g., chlorhexidine) and analgesics (e.g., benzydamine) have been carried out.

Microemulsions

Microemulsions are lipid-based pharmaceutical systems that show significant promise in enhancing drug penetration through the skin. While both microemulsions and nanoemulsions consist of mixtures of typically immiscible liquids-namely oil and water, they exhibit notable differences. Microemulsions are a type of oil-in-water (o/w) emulsion that is thermodynamically stable, with average droplet sizes ranging from approximately 100 to 400 nm. The inclusion of an inner oil phase in these systems facilitates the effective solubilization of lipophilic drugs, resulting in high encapsulation rates, which are essential for optimal drug delivery.

Nanoemulsions, like microemulsions, are colloidal dispersions of oil, water, and surfactants; however, they differ in stability and droplet size. Nanoemulsions are kinetically stable but thermodynamically unstable, with droplet sizes typically ranging from 20 to 200 nm, enabling greater surface area and enhanced drug permeation through the stratum corneum. Unlike microemulsions,

which form spontaneously, nanoemulsions require high-energy methods such as ultrasonication or high-pressure homogenization. In transdermal delivery, nanoemulsions have shown superior efficacy in enhancing skin penetration, improving bioavailability, and enabling sustained release of lipophilic drugs. Their lower surfactant concentrations and minimal skin irritation make them suitable for long-term topical use. Overall, nanoemulsions offer a promising platform for efficient and safe dermal drug delivery.

This method offers distinct advantages for delivering poorly water-soluble compounds through the skin, particularly by bypassing first-pass metabolism, a significant hurdle associated with oral administration. In treating skin-related conditions, topical delivery is favored as it minimizes overall drug usage and potential side effects while providing precise targeting of the intended site of action. Thus, both nano emulsions and microemulsions serve as versatile platforms for drug delivery across lipophilic barriers. These delivery systems have been utilized for various synthetic and natural compounds, enhancing stability, drug delivery efficiency, and bioactivity[37].

Table 2. Common techniques for the characterization of nanoparticles.

Technique	Subtype	Information provided	References
Spectroscopy	UV–visible	Optical properties, synthesis, and stability of NPs	38,39
	FTIR	Investigate e.g. phytochemicals' role in NP synthesis	40,41
	DLS	Determine hydrodynamic diameter, polydispersity index of NPs	41,42
X ray-based	XRD, XAS, XRF, XPS	Determine crystalline structure and particle size of NPs	43
Microscopy	AFM	Surface morphology, shape, size, electrical, and mechanical properties of NPs	44
	SEM	Particle size distribution, morphology and topography of NPs	45,46
	TEM	Morphology, shape, size, elemental composition and electrical conductivity of NPs	47

Optimizing nanoparticle selection and topical formulations for URTI treatment

Clinical evidence supports these pharmacological profiles, underscoring the necessity of choosing the appropriate nanoparticle based on its efficacy, safety for target organs or cells, and cost-effectiveness. Moreover, optimal topical formulations such as nasal sprays, throat rinses, or gels can be developed to enhance delivery for the treatment and prevention of upper respiratory infections (URTIs).

Table 3 compares copper, gold, and silver nanoparticles based on their mechanisms, efficacy, safety, target cells, topical applications, and costs. Copper nanoparticles offer moderate efficacy through membrane disruption but face

cytotoxicity risks at high doses despite their low cost. Gold nanoparticles provide high efficacy in drug delivery and antiviral activity but are limited by high production costs and unclear long-term safety. Silver nanoparticles stand out with broad-spectrum antimicrobial properties, a favorable safety profile at controlled doses, and moderate cost, making them ideal for versatile topical applications like nasal sprays and throat rinses. The summarized information is presented in Fig. 1.

In assessing the most appropriate metal nanoparticles for the treatment and prevention of URTIs,[48-50] it is crucial to examine the distinct profiles of copper, gold, and silver. Copper nanoparticles exhibit moderate antimicrobial efficacy, primarily through the disruption of microbial cell membranes and the induction of oxidative stress. However, their cytotoxicity at elevated concentrations raises safety concerns, particularly for sensitive tissues like the respiratory epithelium. While their low cost presents an attractive option, these safety limitations restrict their broader application in URTI management. Gold nanoparticles demonstrate high efficacy, especially in enhancing drug delivery and antiviral activity. Their mechanism involves interfering with viral replication, making them strong candidates for targeted therapies.[51,52] Despite their generally favorable safety profile, there is limited research on their long-term effects, and their high production costs pose challenges for widespread use, particularly in cost-sensitive healthcare settings.

In contrast, silver nanoparticles emerge as the most well-rounded option across all evaluated criteria.[53] They exhibit high efficacy with broad-spectrum antimicrobial and antiviral properties, functioning by disrupting microbial cell walls and inhibiting critical enzymatic activities. Their safety profile is advantageous when utilized at controlled doses, and although some concerns regarding toxicity at higher concentrations exist, these can be managed with appropriate formulation strategies. Notably, silver nanoparticles offer a cost-effective alternative compared to gold nanoparticles while providing similar or even superior therapeutic outcomes.

Silver nanoparticles: optimal formulations for cost-effective URTI treatment and prevention

AgNPs emerge as the most promising option for advancing the management of URTIs. Their strong antimicrobial and antiviral efficacy, coupled with a favorable safety profile and moderate cost, positions them as ideal candidates for topical applications, such as nasal sprays and throat rinses, providing both treatment and preventive benefits for URTIs. Given the evidence, AgNPs exhibit characteristics that may render them a cost-effective choice for development as a therapeutic agent for URTIs. The next critical step involves determining the most suitable formulation of AgNPs.[54] It is essential to consider the needs of end-users before finalizing product development. Key factors to evaluate from the user's perspective include safety, efficacy, adherence, and cost, priority in that order. A review of the literature reveals several potential topical formulations, each with specific considerations. The most critical aspects to address include ensuring local efficacy without systemic side effects, providing controllable or sustained release, ease of production, and maintaining low costs. Table 4 presents the key considerations necessary for selecting appropriate topical preparation of AgNPs aimed at targeting URTIs.

For targeting the URTIs, AgNPs in the form of nasal sprays and nasal microemulsions are the most promising options.[55,56] Nasal sprays are favored for their high adherence, ease of use, and cost-effectiveness; however, their shorter duration of action may necessitate more frequent applications. On the other hand, nasal

microemulsions, while slightly more complex and costly to produce, offer advantages such as sustained release, enhanced penetration, and prolonged local action. These features can significantly improve long-term efficacy while minimizing systemic side effects. Both formulations represent a favorable balance between safety, efficacy, and cost, with nasal microemulsions providing additional benefits through sustained therapeutic action and improved bioavailability.

Table 3 Profiles of metal nanoparticles for URTIs.

Nanoparticle metal	Mechanism of action	Efficacy in URTI treatment and prevention	Safety profile	Target organs or cells	Suitable topical preparations	Cost considerations
Copper	Disrupts microbial cell membranes, induces oxidative stress	Moderate efficacy with antimicrobial effects against bacteria and viruses	Cytotoxic at higher concentrations	Respiratory epithelial cells, nasal mucosa	Nasal sprays, inhalable particles	Low cost; cost-effective option
Gold	Enhances drug delivery, interferes with viral replication	High efficacy in targeted drug delivery and antiviral activity	Generally safe, but long-term effects unclear	Respiratory epithelial cells	Nasal or throat gels, inhalable drug carriers	High production cost; limits widespread use
Silver	Disrupts microbial cell walls, inhibits enzyme functions	High efficacy with broad antimicrobial and antiviral properties	Proven safe in controlled doses, but some toxicity risks	Respiratory and immune cells	Nasal sprays, throat rinses, antimicrobial coatings	Moderate cost; balances efficacy and safety concerns

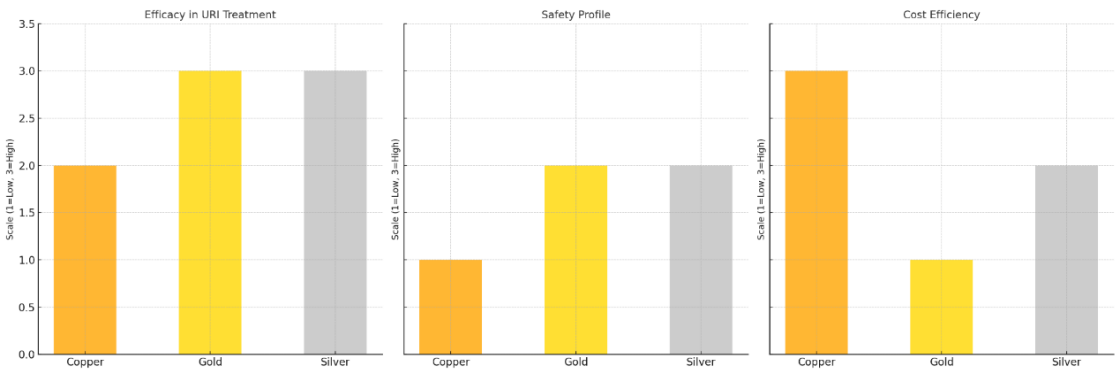

Fig. 1. Comparative analysis of nanoparticle metals for URTI treatment.

Note: This figure compares copper, gold, and silver nanoparticles based on efficacy, safety, and cost efficiency. Gold and silver exhibit high efficacy and better safety profiles, while copper is moderately effective but more cost-efficient. Gold ranks lowest in cost efficiency due to high production costs. This analysis highlights the balance between performance and affordability for optimal selection.

Table 4 Considerations for selecting suitable topical preparations of AgNPs for URTIs.

Topical preparation	Safety	Efficacy	Adherence (Ease of use)	Cost-effectiveness	Other key considerations
Nasal spray	Generally safe for localized application	Effective in delivering nanoparticles to nasal mucosa	High adherence; easy to use	Low cost; simple production process	Limited duration of action; may require frequent reapplication
Throat rinse	Safe when formulated at proper doses	Effective for short-term, localized action	Moderate adherence: regular use required	Low to moderate cost	Short-lived effect; may not ensure sustained release
Nasal gel	Safe, potential for prolonged contact time	High efficacy due to prolonged mucosal adhesion	Moderate adherence; less convenient than spray	Moderate cost; more complex to produce	Allows sustained release; may improve long-term efficacy
Inhalable particles	Generally safe; potential systemic absorption concerns at high doses	Effective for both upper and lower respiratory tract	High adherence; easy to use with correct device	Moderate to high cost due to device requirement	Higher risk of systemic effects; complex formulation and device necessary
Nasal microemulsion	Safe with controlled release properties	Effective with potential for prolonged local action	High adherence; easy to apply	Moderate cost; more complex to produce	Provides sustained release; enhances penetration and bioavailability

Conclusion

In conclusion, the persistent global burden of URTIs highlights an urgent need for effective therapeutic and preventive strategies, particularly those involving targeted topical agents. Despite the widespread use of antibiotics for bacterial infections and symptomatic treatments for viral cases, a critical gap remains in approved topical therapies capable of addressing both microbial pathogens and the associated inflammatory responses. The integration of metal nanoparticles, especially AgNPs, offers a promising solution to this unmet need. AgNPs have demonstrated potent antimicrobial and antiviral activity, a favorable safety profile when properly dosed, and moderate production costs, making them ideal candidates for innovative topical formulations such as nasal sprays and microemulsions. These delivery systems enhance localized therapeutic action, improve patient adherence, and minimize systemic side effects.

To maximize the clinical potential of AgNP-based therapies, future research must prioritize the design of large-scale, rigorously controlled clinical trials to validate their efficacy and safety in diverse populations. Equally important is the development of standardized clinical protocols that provide clear guidance for their practical application. These protocols should encompass optimal dosing regimens,

duration of use, safety monitoring measures, and criteria for patient selection and exclusion. Additionally, comprehensive guidelines should address potential risks, adverse events, and post-treatment follow-up strategies to ensure the safe and effective integration of AgNP therapies into clinical practice.

By focusing on patient-centered formulation strategies-optimizing delivery, safety, adherence, and cost-effectiveness, researchers and clinicians can bridge the current therapeutic gap in URTI management. The successful development and implementation of AgNP-based treatments have the potential to significantly improve patient outcomes and contribute to more robust, comprehensive approaches in respiratory care, ultimately transforming the clinical landscape of URTI treatment.

Conflicts of interest

The authors declare no conflict of interest.

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