Pharmacogn. Res., 2026; 18(3):801-814.
https://www.phcogres.com

Original Article

Recent Advances in Controlling of Urinary Tract Infecting Pathogens Using Metal Nanoparticles and Nanocomposites

Bhakkia Rani Rajendran, Rajeshkumar Shanmugam*, Sulochana Govindharaj

Department of Anatomy, Nanobiomedicine Lab, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, INDIA.

ABSTRACT

Urinary Tract Infections (UTIs) are among the most prevalent bacterial infections worldwide, often complicated by antibiotic resistance, biofilm formation, and high recurrence rates. Conventional treatment strategies are increasingly challenged by multidrug-resistant pathogens, underscoring the urgent need for novel and effective therapeutic approaches. Recent advancements in nanotechnology have introduced promising alternatives through the development of metal nanoparticles and nanocomposites with potent antimicrobial properties. This review highlights the mechanisms by which nanoparticles exert bactericidal effects-such as membrane disruption, Reactive Oxygen Species (ROS) generation, and metal ion release-and discusses the antimicrobial potential of silver, copper, zinc oxide, selenium, and iron oxide nanoparticles. Furthermore, the integration of nanoparticles into polymeric and hydrogel-based nanocomposites has demonstrated synergistic effects that enhance antimicrobial efficacy and biofilm inhibition. Application-based strategies, including nanoparticle-coated urinary catheters, smart controlled-release systems, and nanosensor-enabled diagnostics, are reshaping the clinical landscape of UTI management. While the future of nanotechnology in UTI treatment is promising, challenges such as nanoparticle toxicity, stability, and regulatory standardization must be addressed. Emphasizing safety, biocompatibility, and sustainability will be essential for successful clinical translation. Collectively, this review underscores the transformative potential of nanotechnology to revolutionize UTI prevention, diagnosis, and treatment.

Keywords: Antimicrobial Resistance, Nanocomposites, Nanoparticles, Targeted Drug Delivery, Urinary Tract Infections (UTIs).

Correspondence:
Dr. Rajeshkumar Shanmugam
Professor and Chief Scientist, Department of Anatomy, Nanobiomedicine Lab, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai-602105, Tamil Nadu, INDIA.
Email: rajeshkumars.sdc@saveetha.com

Received: 22-12-2025;
Revised: 19-01-2026;
Accepted: 09-03-2026.

INTRODUCTION

Urinary Tract Infections (UTIs) are among the most common infectious diseases globally, affecting millions of individuals each year. They represent a significant public health concern due to their high incidence, recurrence rates, and associated healthcare costs. UTIs are characterized by the colonization and proliferation of pathogenic microorganisms within the urinary system, encompassing the urethra, bladder, ureters, and kidneys (Pietropaolo *et al*., 2018). While UTIs can affect both sexes, women are disproportionately impacted due to anatomical and physiological factors, with estimates suggesting that nearly 50-60% of women experience at least one episode of UTI in their lifetime (Smith and Jabal, 2023).

DOI: 10.5530/pres.20260190

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

The primary causative agents of UTIs are Gram-negative bacteria, with *Escherichia coli* accounting for 80-90% of community-acquired infections. Other uropathogens include *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis*, *Staphylococcus saprophyticus*, and *Pseudomonas aeruginosa* (Fuochi *et al*., 2024). These pathogens adhere to the uroepithelial lining, form biofilms, and often exhibit virulence mechanisms that facilitate persistent infection and resistance to host immune responses. Hospital-Acquired UTIs (HAUTIs), particularly those associated with urinary catheter use, contribute significantly to the morbidity and mortality of hospitalized patients, especially those in intensive care settings (Krajewski *et al*., 2024: Gandhi *et al*., 2024).

Traditional approaches to UTI treatment have primarily relied on the empirical use of antibiotics, including trimethoprim-sulfamethoxazole, nitrofurantoin, and fluoroquinolones. However, the widespread and often indiscriminate use of these antimicrobials has led to the alarming rise of Antimicrobial Resistance (AMR) (Crintea *et al*., 2023). Multi-Drug-Resistant (MDR) strains of *E. coli*, *Klebsiella*, and *Pseudomonas* have emerged as formidable clinical challenges, reducing therapeutic options and leading to recurrent,

complicated, or treatment-refractory infections. Compounding the issue is the delay in diagnosis due to conventional laboratory methods, which require time for culture growth and antibiotic susceptibility testing (Franco *et al.*, 2025; Mohammed *et al.*, 2025).

In light of these challenges, there is a pressing need for alternative or adjunctive strategies that can overcome microbial resistance, prevent biofilm formation, and enhance therapeutic efficacy without inducing significant toxicity or resistance development. Nanotechnology offers a revolutionary platform in this context (Sadredinamin *et al.*,2025). Metal-based Nanoparticles (NPs), including Silver (AgNPs), Zinc Oxide (ZnO NPs), Copper Oxide (CuO NPs), Gold (AuNPs), and Iron Oxide (Fe_2O_3 NPs), exhibit potent antimicrobial activity against a wide spectrum of uropathogens (Foxman *et al.*, 2025) Their nano-scale size enables intimate interactions with bacterial membranes, while their physicochemical properties allow for multiple mechanisms of action-such as disruption of bacterial cell walls, interference with DNA replication, inhibition of enzyme function, and generation of Reactive Oxygen Species (ROS) (Badran *et al.*, 2025; Kloft *et al.*, 2025).

Furthermore, the development of nanocomposites-hybrid materials composed of metal nanoparticles embedded in biocompatible matrices such as polymers, hydrogels, or carbon-based structures has expanded the functional capabilities of nanomaterials (Bradley *et al.*, 2025). These systems not only enhance the stability and bioavailability of nanoparticles but also allow for targeted drug delivery, sustained release, and synergistic effects with conventional antimicrobials. Emerging strategies also include nanoparticle coatings on catheters to prevent biofilm formation, nano-encapsulated herbal or phytochemical agents for combination therapies, and light-activated nanomaterials for photodynamic antimicrobial therapy (Ismail *et al.*, 2025; Gupta *et al.*, 2025).

Despite the encouraging evidence from *in vitro* studies and animal models, several hurdles remain in translating nanotechnology-based interventions into clinical settings (Guo *et al.*, 2025). Concerns regarding toxicity, biodistribution, long-term safety, and regulatory approval must be addressed through rigorous research and validation. Nevertheless, the growing body of evidence underscores the potential of nanoscale materials as game-changers in the management of UTIs (Raheem *et al.*, 2025; Odunmbaku, 2025).

This review comprehensively discusses the current landscape of UTIs, emphasizing the epidemiology, causative organisms, and challenges associated with existing therapies. It then delves into recent advances in the use of metal nanoparticles and nanocomposites, highlighting their mechanisms of antimicrobial action, formulation strategies, and preclinical applications. Through this synthesis, the review aims to provide insights into the evolving role of nanotechnology in combatting urinary tract infections and to identify future directions for research and clinical translation.

Pathogenesis and Common Pathogens of UTIs

Mechanism of infection and colonization

Urinary Tract Infections (UTIs) are caused primarily by the colonization of uropathogens within the urinary tract, leading to inflammation and infection. Figure 1. The pathogenesis of UTIs is a multistep process that begins with the adhesion of pathogenic bacteria to the uroepithelial lining. Uropathogenic *Escherichia coli* (UPEC), the most prevalent causative agent, utilizes specialized surface structures such as type 1 fimbriae to bind to mannose-containing glycoproteins on bladder epithelial cells (Liao *et al.*, 2025). This adhesion is a crucial initial step that allows pathogens to resist urinary flushing and establish colonization. Following adhesion, some bacteria can invade the superficial urothelium and form intracellular bacterial communities, offering protection from both host immune responses and antibiotic treatments (Dziuba *et al.*, 2025).

To sustain infection, uropathogens employ sophisticated immune evasion strategies. UPEC, for example, can downregulate the host immune response by suppressing cytokine production, including Interleukin-6 (IL-6), thereby delaying inflammatory signaling and immune cell recruitment (Sajeevan *et al.*, 2025). This immune evasion facilitates prolonged survival and replication within the urinary tract. Additionally, many uropathogens have the ability to form biofilms-structured communities of bacterial cells embedded in a self-produced extracellular matrix (Zhang *et al.*, 2024). These biofilms form either on uroepithelial surfaces or indwelling medical devices such as catheters, providing a protective environment that significantly enhances bacterial survival and resistance to antibiotics (Zuo *et al.*, 2024).

Frequently implicated pathogens

Among the various pathogens implicated in UTIs, *E. coli* accounts for approximately 80-90% of community-acquired cases. UPEC strains are well-adapted to the urinary environment due to their virulence arsenal, which includes adhesins, toxins, siderophores, and iron-acquisition systems. *Klebsiella pneumoniae*, another significant uropathogen, is increasingly associated with both community and hospital-acquired infections and is particularly concerning due to its propensity to develop Extended-Spectrum Beta-Lactamase (ESBL) resistance (Köhn *et al.*, 2024). *Proteus mirabilis* contributes to complicated UTIs through its urease activity, which increases urinary pH and promotes the formation of struvite stones. *Pseudomonas aeruginosa*, known for its multidrug resistance and biofilm-forming ability, is commonly isolated in catheter-associated UTIs. *Enterococcus faecalis*, a Gram-positive bacterium, often causes nosocomial infections and presents challenges due to its resistance to commonly used

antimicrobials, including vancomycin (Aljanabi, 2025; Ouyang *et al.*, 2024).

Biofilm formation and antimicrobial resistance patterns

The formation of biofilms by these pathogens plays a central role in persistent and recurrent infections. Within the biofilm matrix, bacteria adopt altered metabolic states, exhibit reduced growth rates, and become substantially more resistant to antimicrobial agents. This biofilm-associated resistance is not merely due to the physical barrier created by the extracellular matrix but also involves physiological changes in the bacterial cells, such as the expression of efflux pumps and stress response genes (Rima *et al.*, 2025). Furthermore, biofilms serve as hotspots for horizontal gene transfer, facilitating the spread of antibiotic resistance genes among cohabiting bacteria.

The rise of antimicrobial resistance among UTI pathogens, particularly in *E. coli* and *Klebsiella speceies*, further complicates treatment. Resistance mechanisms include the production of beta-lactamases, alterations in antibiotic target sites, decreased membrane permeability, and the activity of efflux pumps (Muratov *et al.*, 2025). These adaptations reduce the efficacy of conventional antibiotics and limit treatment options, particularly for patients with recurrent or complicated UTIs. As a result, there is an urgent need for the development of novel antimicrobial strategies that can effectively target biofilm-embedded bacteria and overcome resistance mechanisms (Williams *et al.*, 2025).

Therefore, the pathogenesis of UTIs is driven by a complex interplay of microbial virulence, host-pathogen interactions, and immune modulation. The frequent involvement of multidrug-resistant organisms and the protective nature of biofilms underscore the limitations of current therapeutic approaches. A deeper understanding of these pathogenic mechanisms is essential for guiding the development of innovative treatments, such as metal nanoparticles and nanocomposites, that can disrupt bacterial colonization, inhibit biofilm formation, and enhance antimicrobial efficacy in urinary tract infections (Krawczyk and Wityk, 2025).

Limitations of Current Antimicrobial Therapies

The therapeutic landscape for Urinary Tract Infections (UTIs) has long relied on conventional antibiotics; however, several critical limitations have emerged that compromise the efficacy of current antimicrobial strategies. One of the most pressing concerns is the escalating antibiotic resistance crisis. The widespread emergence of Multi-Drug-Resistant (MDR) uropathogens particularly *Escherichia coli* has significantly undermined the effectiveness of commonly used antibiotics such as fluoroquinolones, cephalosporins, and trimethoprim-sulfamethoxazole (Tarek *et al.*, 2024). Studies have reported alarming resistance rates, making empirical treatment increasingly unreliable and prompting the need for regular surveillance of regional resistance trends to inform treatment protocols. As resistance mechanisms such as beta-lactamase production, efflux pump expression, and target-site modification become more prevalent, the therapeutic window for effective intervention continues to narrow (Keenan *et al.*, 2024).

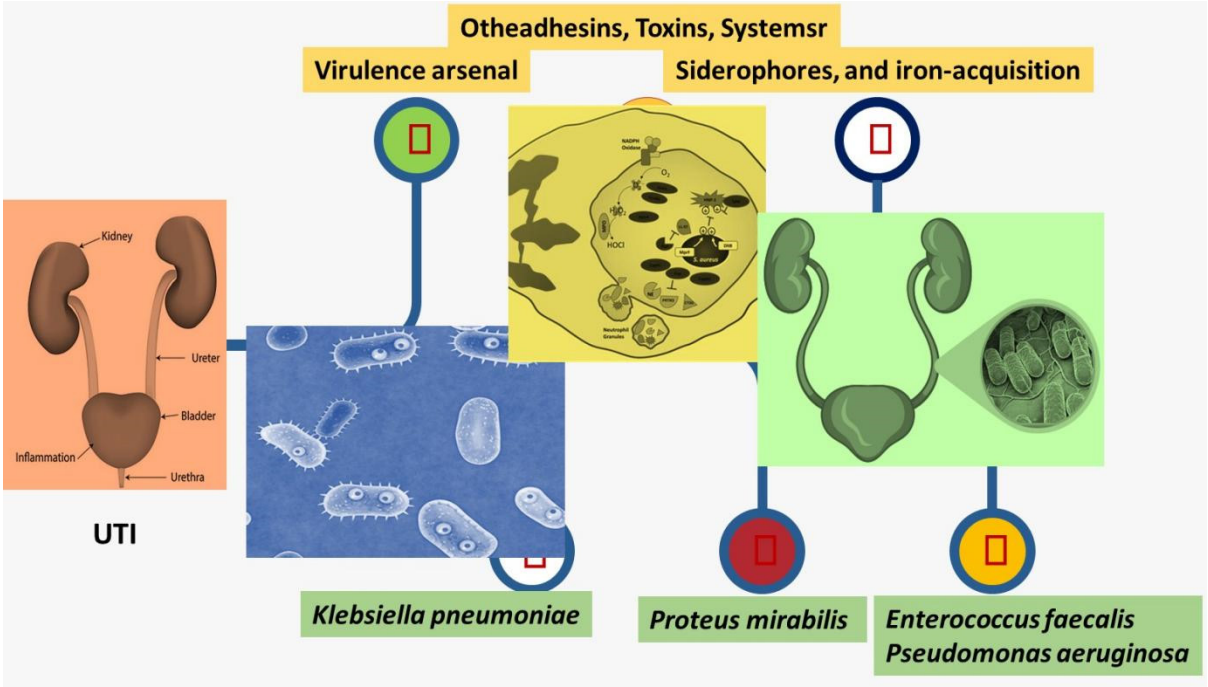

Figure 1: Overview of key uropathogens and their virulence mechanisms involved in Urinary Tract Infections (UTIs).

In addition to resistance, recurrence and chronicity represent major clinical challenges in UTI management. Recurrent Urinary Tract Infections (rUTIs) affect a substantial proportion of patients, often leading to repeated antibiotic exposure, progressive resistance development, and diminished quality of life (Păcurar *et al*., 2025). These recurrent infections may arise from persistent bacterial reservoirs within the uroepithelium, reinfection from the perineal flora, or ineffective eradication due to biofilm formation. Managing chronic or recurrent UTIs typically involves prolonged or repeated antibiotic courses, which increase both treatment costs and the risk of adverse outcomes (Baimakhanova *et al*., 2025).

The long-term use of antibiotics also introduces a range of side effects that limit their desirability as a sustainable therapeutic option. Gastrointestinal disturbances, allergic reactions, and the disruption of normal microbiota are common adverse events associated with extended antimicrobial use. Such disturbances can predispose patients to secondary infections, including *Clostridium difficile colitis*, and contribute to antibiotic fatigue, where patients become less adherent to prescribed regimens due to side effect burden. These issues collectively impact treatment compliance, prolong recovery, and heighten the overall burden on healthcare systems (Godfrey *et al*., 2025).

In light of these limitations, there is a growing consensus on the need to explore and integrate alternative or adjunctive therapies into UTI management frameworks. Phytotherapeutic agents derived from herbal extracts with antimicrobial and anti-inflammatory properties have shown promise in preliminary studies. Likewise, vaccine development targeting specific uropathogenic strains holds potential for reducing UTI incidence, particularly in high-risk populations. Probiotics have also emerged as a strategy to restore microbial balance within the genitourinary tract and inhibit pathogen colonization (Lubbad, 2025). Among these, nanotechnology has garnered significant attention for its ability to enhance antimicrobial delivery, circumvent resistance mechanisms, and target biofilms effectively. Engineered nanoparticles and nanocomposites can be tailored to release drugs at infection sites, disrupt bacterial membranes, and improve drug solubility and stability, making them a valuable adjunct to traditional therapy (Gbegbe *et al*., 2024).

The limitations of current antimicrobial therapies for UTIs ranging from drug resistance and recurrence to adverse effects and treatment failures necessitate the urgent development of more effective, safer, and sustainable alternatives. Innovations in nanomedicine, alongside emerging strategies such as probiotics, vaccines, and phytochemicals, offer a multifaceted approach to overcoming the growing challenges in UTI management. Continued research, clinical validation, and interdisciplinary collaboration will be essential to translate these innovations into accessible and impactful solutions (Rezania *et al*., 2024).

Metal Nanoparticles as Antimicrobial Agents

Mechanisms of antimicrobial action (membrane disruption, ROS generation, metal ion release)

Metal Nanoparticles (MNPs) have emerged as potent antimicrobial agents owing to their distinct physicochemical properties and multiple mechanisms of action. In the face of increasing antibiotic resistance, these nanoscale materials offer a valuable alternative by targeting bacterial cells through pathways that differ fundamentally from those used by conventional antibiotics. Their small size, high surface area-to-volume ratio, and ability to generate reactive species or release toxic ions contribute collectively to their enhanced antimicrobial performance (Franco *et al*., 2024).

One of the primary mechanisms by which metal nanoparticles exert their antibacterial activity is through the disruption of bacterial cell membranes. Upon contact, nanoparticles interact electrostatically with the negatively charged components of the bacterial cell wall, including lipopolysaccharides in Gram-negative bacteria and teichoic acids in Gram-positive strains. This interaction leads to membrane destabilization, increased permeability, and eventual rupture (Dubey *et al*., 2024). The compromised integrity of the bacterial membrane facilitates leakage of intracellular components such as nucleic acids, proteins, and ions, culminating in cell lysis and death. The surface charge of nanoparticles plays a pivotal role in this process, with positively charged particles showing superior efficacy due to their strong affinity for negatively charged bacterial surfaces (Kashyap *et al*., 2024).

Another critical antimicrobial mechanism of MNPs involves the generation of Reactive Oxygen Species (ROS). Upon exposure to biological environments, metal nanoparticles such as Silver (AgNPs), Zinc Oxide (ZnO NPs), and Copper Oxide (CuO NPs) can induce oxidative stress in bacterial cells by catalyzing the production of ROS including Hydroxyl Radicals (•OH), Superoxide Anions (O_2^-), and Hydrogen Peroxide (H_2O_2) (Qi *et al*., 2024). These ROS cause widespread damage to essential cellular structures. Lipid peroxidation disrupts membrane integrity, protein oxidation impairs enzymatic function, and DNA strand breaks interfere with replication and transcription processes (Figure 2). The cumulative oxidative stress overwhelms the bacterial antioxidant defenses, resulting in cellular apoptosis or necrosis (Saba *et al*., 2024).

In addition to physical and oxidative damage, MNPs exhibit antimicrobial properties through the controlled release of metal ions. Many nanoparticles undergo partial dissolution or ion leaching in aqueous environments, liberating biologically active metal ions such as Ag^+, Zn^{2+}, or Cu^{2+}. These ions can interact with thiol groups in bacterial enzymes, impairing metabolic functions, or bind directly to DNA, inhibiting replication (Tharani *et al*., 2023). The released ions can also disrupt ion gradients across

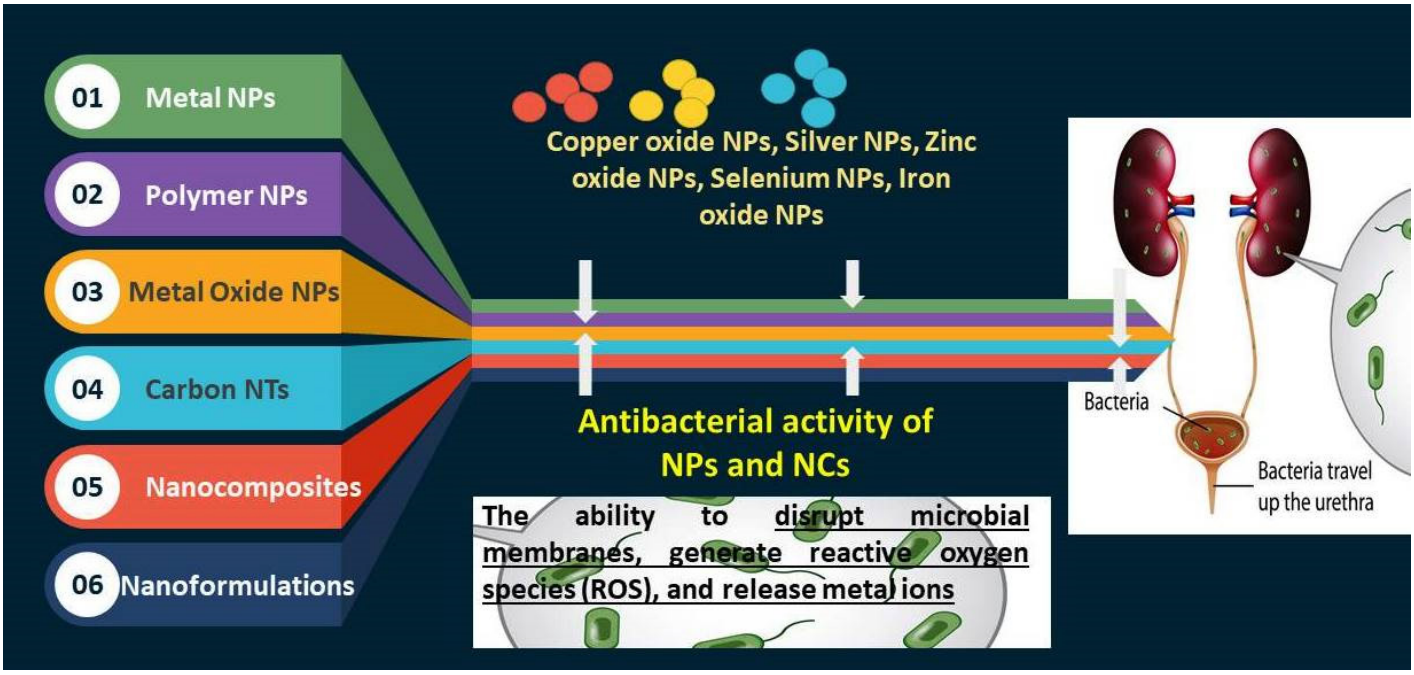

Figure 2: Types of Nanoparticles (NPs) and Nanocomposites (NCs) exhibiting antibacterial activity against Urinary Tract Infections (UTIs).

bacterial membranes and interfere with essential nutrient uptake, further compromising bacterial viability. Notably, the combination of physical disruption, oxidative stress, and ionic toxicity leads to a synergistic antimicrobial effect that enhances the overall potency of MNPs against both planktonic and biofilm-embedded bacterial cells (Singh *et al*., 2025).

In General, metal nanoparticles utilize a multifaceted approach to eliminate pathogenic bacteria. Through membrane destabilization, ROS-mediated oxidative damage, and metal ion release, MNPs offer a broad-spectrum antimicrobial strategy that is difficult for pathogens to resist. These mechanisms work concurrently, making it challenging for bacteria to develop simultaneous resistance. As the global burden of antimicrobial resistance continues to escalate, harnessing the unique properties of metal nanoparticles offers a promising avenue for next-generation antimicrobial agents. Future research should focus on optimizing nanoparticle formulation, enhancing biocompatibility, and minimizing cytotoxicity to ensure their safe and effective application in clinical and biomedical settings (Manikandan *et al*., 2025).

Types of metal nanoparticles studied for UTI pathogens

Numerous types of metal nanoparticles have been investigated for their antimicrobial properties against Urinary Tract Infection (UTI) pathogens. These nanoparticles exhibit diverse mechanisms of action, including membrane disruption, oxidative stress induction, and metal ion release, making them powerful alternatives or adjuncts to traditional antibiotic therapies. Their unique physicochemical properties and ability to overcome resistance mechanisms have led to increasing interest in their application for UTI prevention and treatment (Slavin *et al*., 2022; Mammari *et al*., 2022).

Copper Nanoparticles (CuNPs) are among the most promising due to their cost-effectiveness, broad-spectrum antimicrobial activity, and ease of synthesis using green chemistry approaches. Eco-friendly synthesis methods, such as those utilizing plant extracts like *Cissus vitiginea*, allow for the production of biocompatible and stable CuNPs. These nanoparticles have demonstrated significant antibacterial activity against a wide range of UTI pathogens, including *Escherichia coli, Enterococcus species, Proteus species*, and *Klebsiella species*. The antimicrobial activity of CuNPs is primarily attributed to their ability to disrupt bacterial membranes, induce oxidative stress through the generation of Reactive Oxygen Species (ROS), and release toxic copper ions that interfere with bacterial enzymatic systems and DNA integrity (Wu *et al*., 2020).

Selenium Nanoparticles (SeNPs) have also gained attention for their ability to target antibiotic-resistant strains of uropathogens. Mycogenic synthesis, particularly when combined with gamma irradiation techniques, enhances the stability and antimicrobial potency of SeNPs. These nanoparticles exhibit strong bactericidal effects by inducing ROS production and altering membrane permeability, while also showing potential for use in combination with existing antibiotics to overcome resistance. The low toxicity of selenium to human cells further supports its promise as a safe and effective agent for UTI therapy (Manyawu *et al*., 2024).

Silver Nanoparticles (AgNPs) are perhaps the most extensively studied metal nanoparticles in antimicrobial research due to their potent and broad-spectrum activity. AgNPs exert their antimicrobial effects through multiple pathways, including the

release of silver ions, which bind to thiol groups in bacterial proteins, disrupt cellular membranes, and induce oxidative stress. These actions collectively lead to bacterial death. The efficacy of AgNPs against both Gram-negative and Gram-positive uropathogens, along with their synergistic effects when combined with antibiotics, makes them valuable candidates for managing UTIs, especially in cases involving multi-drug-resistant strains (El-Sayyad *et al*., 2020; Pauline *et al*., 2025).

Zinc Oxide Nanoparticles (ZnO NPs) are another class of metal-based nanomaterials with significant potential in UTI control. These nanoparticles demonstrate excellent antibacterial activity by generating ROS, damaging bacterial membranes, and interfering with intracellular components. ZnO NPs are particularly useful in biomedical applications due to their low toxicity and high biocompatibility. They can be incorporated into hydrogels, creams, or catheter coatings to prevent bacterial colonization and reduce the incidence of Catheter-Associated Urinary Tract Infections (CAUTIs). Their multifunctional properties also enable sustained antimicrobial activity at infection sites (Li *et al*., 2023).

Iron Oxide Nanoparticles (Fe_2O_3 NPs) have been explored for their dual function as antimicrobial agents and drug delivery vehicles. These nanoparticles can generate ROS and disrupt microbial metabolism, contributing to direct antimicrobial effects. Moreover, their magnetic properties enable targeted delivery of antibiotics, enhancing drug accumulation at infection sites while minimizing systemic toxicity. Fe_2O_3 NPs may also work synergistically with existing antimicrobial agents, improving their penetration into biofilms and enhancing overall therapeutic outcomes against persistent UTI pathogens (Al-Enizi *et al*., 2018).

Overall, metal nanoparticles including copper, selenium, silver, zinc oxide, and iron oxide represent a diverse and potent arsenal of antimicrobial agents capable of addressing the complex challenges of urinary tract infections. Each type offers unique benefits in terms of mechanism of action, biocompatibility, and potential for integration into advanced therapeutic formulations. Their continued exploration and development may offer effective, non-conventional strategies for controlling UTIs, particularly in the context of rising antibiotic resistance and biofilm-related complications (Zhong *et al*., 2025; Liu *et al*., 2022).

Nanocomposites for Enhanced Antimicrobial Activity

Nanocomposites have emerged as a transformative solution in antimicrobial research, offering enhanced functional properties through the combination of nanoparticles and matrix materials. These composite systems synergistically integrate the advantages of both components typically metal or metal oxide nanoparticles and polymeric or hydrogel matrices to create multifunctional materials with superior physicochemical and biological characteristics. Their tunable structures, coupled with the ability to exhibit sustained and targeted antimicrobial activity, make them particularly valuable in the context of Urinary Tract Infection (UTI) prevention and treatment (Unal *et al*., 2024).

By definition, nanocomposites are structured materials wherein nanoparticles are uniformly dispersed within a continuous matrix. This matrix, often composed of polymers such as polyethylene, polylactic acid, or natural polysaccharides, provides structural integrity, mechanical strength, and biocompatibility. When metal-based nanoparticles such as Silver (AgNPs), Zinc Oxide (ZnO NPs), Copper Oxide (CuO NPs), or bimetallic particles are embedded into these matrices, the resulting nanocomposite demonstrates amplified antimicrobial efficacy (Cuadra *et al*., 2022). The nanoparticles contribute unique functionalities, including the ability to disrupt microbial membranes, generate Reactive Oxygen Species (ROS), and release metal ions with bactericidal properties. The matrix, on the other hand, facilitates the controlled release of these active agents while maintaining a stable and application-friendly format (Dwivedi *et al*., 2024).

Polymer-metal nanoparticle hybrids represent one of the most commonly employed forms of antimicrobial nanocomposites. In these systems, nanoparticles are physically or chemically integrated into synthetic or natural polymer networks (Kazantsev *et al*., 2022). Silver nanoparticle-based polymer composites, for example, have been extensively studied for their high antibacterial efficiency, structural stability, and prolonged ion release. Such materials are widely applied as coatings for urinary catheters and other medical devices, where their ability to prevent biofilm formation is particularly critical in reducing Catheter-Associated Urinary Tract Infections (CAUTIs). These hybrids not only enhance antimicrobial activity but also improve the durability and flexibility of the materials in clinical use (Al-Gaashani *et al*., 2023).

Hydrogel-nanoparticle composites, another important class of antimicrobial nanocomposites, combine hydrophilic polymer matrices with embedded nanoparticles to create moisture-retaining, biocompatible systems ideal for drug delivery and wound healing applications. These hydrogels can be synthesized via in situ polymerization or physical blending, leading to materials capable of releasing therapeutic agents in a controlled and sustained manner (Kumar *et al*., 2022). The incorporation of metal nanoparticles into hydrogels results in composites that provide localized antimicrobial action, reduced cytotoxicity, and enhanced healing potential. Their application in intravesical therapies or as coatings for urinary catheters presents a promising strategy for managing infections without systemic side effects (Przybyłek *et al*., 2019).

The antimicrobial effects of nanocomposites are often further enhanced by the synergistic action of multiple nanoparticles within a single matrix. Bimetallic nanocomposites, such as Copper-Zinc Oxide (Cu-ZnO), exemplify this synergy by combining distinct antimicrobial pathways from each metal. These multi-metal

systems can disrupt bacterial cell membranes more efficiently, generate higher levels of ROS, and release a broader spectrum of toxic metal ions (Pinzari *et al*., 2024). Similarly, multi-component nanocomposites incorporating carbon nanotubes, graphene oxide, or phytochemical agents alongside metal nanoparticles have shown superior antibacterial activity against UTI-causing pathogens due to enhanced interaction with microbial surfaces and increased oxidative stress induction (Kováčová *et al*., 2022).

In general, nanocomposites offer a highly adaptable platform for developing next-generation antimicrobial materials aimed at controlling urinary tract infections. Their ability to combine structural and functional properties through the integration of metal nanoparticles with polymers or hydrogels enables the creation of materials that are not only mechanically robust and biocompatible but also highly effective in eradicating uropathogens. As antibiotic resistance continues to challenge conventional treatment strategies, nanocomposites stand out as a powerful tool in the design of targeted, localized, and sustainable antimicrobial therapies for UTIs.

Recent *in vitro* and *in vivo* Studies

Recent advances in nanotechnology have led to a surge in preclinical research focusing on the antimicrobial efficacy of metal nanoparticles and nanocomposites against Urinary Tract Infection (UTI) pathogens. A growing body of evidence from both *in vitro* and *in vivo* studies supports their potential as alternative or adjunctive therapies, particularly in the face of rising antibiotic resistance and the need for biofilm-targeted strategies (Sahu *et al*., 2025). These studies explore not only their comparative antibacterial activity but also their impact on biofilm formation and their cytotoxicity toward mammalian cells, laying the groundwork for potential clinical applications (Mwaheb *et al*., 2021).

Preclinical investigations have highlighted the significant antibacterial properties of metal oxide nanoparticles such as Copper Oxide (CuO) and Zinc Oxide (ZnO) against a range of UTI pathogens, particularly *Escherichia coli* (Francis *et al*., 2023). These biogenic nanoparticles, synthesized using eco-friendly methods, have demonstrated strong antimicrobial effects under both dark and light conditions, indicating their versatility and potential for therapeutic application in diverse clinical scenarios. Their ability to generate Reactive Oxygen Species (ROS), penetrate bacterial biofilms, and disrupt cellular membranes has been repeatedly validated across various laboratory models (Rajaram *et al*., 2024).

In comparative studies, Silver Nanoparticles (AgNPs) synthesized using *Lantana camara* leaf extract have shown potent activity against a broad spectrum of UTI pathogens, including *E. coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. The antimicrobial efficacy of these green-synthesized AgNPs was quantified through Zone of Inhibition (ZOI) assays, with the highest ZOI recorded at 21 mm against *E. coli*, underscoring their strong bactericidal potential (Ramteke *et al*., 2020). Similarly, zinc oxide nanoparticles, especially those doped with cadmium, have displayed remarkable activity against Gram-negative and Gram-positive bacteria. Their ability to induce membrane leakage and structural damage correlates strongly with their enhanced antimicrobial potency. In addition, studies involving copper and zinc oxide nanoparticles in combination have shown synergistic antimicrobial effects, achieving over 90% inhibition of key pathogens, including multidrug-resistant strains such as Methicillin-Resistant *Staphylococcus aureus* (MRSA). These findings emphasize the benefits of bimetallic or hybrid nanocomposite systems in enhancing the spectrum and strength of antibacterial action (Gutiérrez-Santana *et al*., 2024; Palei *et al*., 2020).

Biofilm formation remains a critical barrier in the treatment of chronic and recurrent UTIs, and nanoparticles have shown considerable promise in addressing this issue. Silver nanoparticles have been reported to effectively disrupt pre-formed biofilms by *E. coli*, interfering with the extracellular matrix and bacterial adhesion (Sharma *et al*., 2022). These findings are significant given that biofilms can reduce antibiotic susceptibility by several orders of magnitude. Moreover, *in vivo* studies using animal models have begun to validate the ability of certain nanoparticles to not only inhibit biofilm formation but also eradicate established biofilms. Such findings point to their potential utility in managing Catheter-Associated Urinary Tract Infections (CAUTIs), where biofilm-related complications are prevalent (Yao *et al*., 2022; Subash *et al*., 2024).

Equally important to their antimicrobial performance is the cytotoxicity and biocompatibility profile of these nanoparticles. Preclinical assessments using human cell lines have shown that silver and zinc oxide nanoparticles exhibit relatively low cytotoxicity at therapeutic concentrations (Wu *et al*., 2024). Their safety profiles are further supported by biocompatibility assays, which suggest that metal nanoparticles can be safely integrated into drug delivery systems, hydrogels, and medical device coatings without causing significant harm to host tissues. These findings are vital for clinical translation, as they demonstrate a favorable balance between antibacterial efficacy and cellular safety (Goda *et al*., 2021).

Therefore, the collective results of both recent *in vitro* and *in vivo* studies affirm the potential of metal nanoparticles and nanocomposites as viable antimicrobial agents against UTI pathogens. Their capacity to inhibit pathogen growth, eradicate biofilms, and maintain low cytotoxicity establishes a solid foundation for their future application in urinary tract infection management. Continued research is essential to further elucidate their mechanisms of action, optimize their formulations, and validate their efficacy in human clinical trials (Cao *et al*., 2025; Xiao *et al*., 2024).

Application-Based Strategies

Recent advancements in nanotechnology have paved the way for a wide range of application-based strategies to prevent, manage, and treat Urinary Tract Infections (UTIs). These approaches utilize the unique properties of nanomaterials including their high surface area, tunable surface chemistry, and ability to penetrate biological barriers to develop targeted, effective, and patient-centered solutions. In particular, nanomaterial-based interventions have shown significant promise in minimizing the burden of Catheter-Associated UTIs (CAUTIs), improving localized drug delivery, and enhancing diagnostic capabilities in real time (Tenke *et al*., 2014).

One of the most promising applications of nanotechnology in UTI management is the development of catheter coatings engineered with antimicrobial nanomaterials. Bio-inspired coatings, such as those based on metal-catechol-assisted mussel chemistry, have enabled the functionalization of catheter surfaces with Antimicrobial Peptides (AMPs) (Yao *et al*., 2022). These coatings mimic natural adhesion mechanisms to anchor AMPs onto the catheter, providing a robust antimicrobial barrier that inhibits bacterial attachment, suppresses biofilm formation, and prevents encrustation caused by urease-producing bacteria. By reducing the likelihood of obstruction and infection, such coatings extend catheter usability and reduce the need for frequent replacements (Ghanwate *et al*., 2012). Similarly, nanodrug-loaded hydrogel coatings have emerged as effective solutions for catheter-based infection prevention. These hydrogels incorporate metal or metal oxide nanoparticles that steadily release antimicrobial agents, such as silver or copper ions, to provide continuous protection against uropathogens like *E. coli*. Compared to traditional antimicrobial coatings, these nanoparticle-infused hydrogels offer superior efficacy and prolonged antibacterial action, making them ideal for long-term catheterization scenarios (Fernández Llamas *et al*., 2025).

Intravesical therapies formulated with nanoparticles offer another innovative strategy for UTI treatment. These systems are designed to deliver antimicrobial agents directly into the bladder, thereby achieving higher local drug concentrations and minimizing systemic exposure. Nanoformulated drug delivery systems such as liposomes, polymeric nanoparticles, or nanogels can be engineered to enhance mucoadhesion and prolong retention time within the bladder environment (Putta *et al*., 2024). Furthermore, sustained-release systems using nanocarriers have been developed to encapsulate antiseptics like chlorocresol or benzoic acid. These formulations demonstrate long-lasting antibacterial activity, reducing bacterial colonization on catheter surfaces over extended periods. The local and sustained nature of these therapies not only improves therapeutic outcomes but also minimizes adverse effects associated with systemic antibiotic administration (Minnema *et al*., 2022; Sajadimajd *et al*., 2022).

Controlled release nano-systems represent a significant advancement in smart drug delivery for UTI management. These systems can be programmed to respond to specific stimuli in the urinary tract such as changes in pH, enzymatic activity, or temperature to release therapeutic agents in a time-dependent or condition-specific manner (Dorababu, 2019). This targeted approach ensures that antimicrobial agents are delivered precisely when and where they are needed, improving efficacy while reducing toxicity and preserving the healthy microbiota. In addition to enhancing drug delivery, these systems also contribute to clinical biosecurity by maintaining effective antimicrobial concentrations over time, which in turn reduces the need for repeated catheter interventions and decreases the likelihood of recurrent infections (Jhang *et al*., 2021).

The diagnostic potential of nanotechnology has also been harnessed through the development of nanosensor-based point-of-care systems. These nanosensors are capable of detecting UTI pathogens with high sensitivity and specificity, enabling rapid and accurate diagnosis at the bedside (Girard *et al*., 2015). By incorporating nanomaterials such as gold nanoparticles, carbon nanotubes, or quantum dots, these sensors achieve enhanced signal amplification, facilitating the real-time monitoring of bacterial load and antibiotic resistance profiles. This allows for early intervention and the implementation of personalized treatment strategies tailored to the patient's infection dynamics. Moreover, the integration of these sensors into wearable or implantable devices has the potential to revolutionize UTI monitoring and management, particularly in high-risk or hospitalized patients (Leblebicioglu, 2003; Urinary Tract Infection Study Group, 1987).

In summary, application-based strategies employing nanomaterials are reshaping the landscape of urinary tract infection prevention and treatment. From antimicrobial catheter coatings and intravesical therapies to controlled release systems and advanced diagnostics, nanotechnology offers multifaceted solutions that address the clinical challenges associated with UTIs. These innovations not only enhance antimicrobial efficacy and patient outcomes but also reduce healthcare-associated complications, particularly in catheterized individuals. As research progresses, the optimization and clinical translation of these nanotechnology-enabled applications will be critical in advancing next-generation therapies for urinary tract infections.

Challenges and Considerations

The integration of nanotechnology into antimicrobial strategies for Urinary Tract Infections (UTIs) holds significant therapeutic potential. However, the clinical translation of nanoparticle-based approaches is not without challenges. To ensure safety, efficacy, and long-term viability, several critical considerations must be addressed. These include concerns about toxicity and biocompatibility, nanoparticle stability, regulatory complexities,

and the risk of microbial resistance to nanomaterials (Zhang *et al*., 2023).

One of the foremost concerns in nanomedicine is the potential toxicity of nanoparticles to human tissues. While metal nanoparticles such as silver, zinc oxide, and copper oxide exhibit potent antimicrobial effects, studies have demonstrated that at high concentrations or prolonged exposure, these nanoparticles may induce cytotoxic effects in mammalian cells. Such effects include oxidative stress, mitochondrial dysfunction, and DNA damage, which can lead to apoptosis or inflammation (Bassetti *et al*., 2023). Therefore, ensuring biocompatibility remains a priority in nanoparticle design. Surface modifications, appropriate dosing, and the use of biodegradable carriers are strategies employed to balance antimicrobial efficacy with minimal cytotoxicity. Comprehensive preclinical toxicity assessments, including *in vitro* cytotoxicity assays and *in vivo* biocompatibility studies, are essential for determining safe therapeutic thresholds (Patra *et al*., 2024; Sánchez*et al*., 2021).

Stability and aggregation of nanoparticles in biological environments represent another major challenge. In physiological conditions, nanoparticles may encounter variable pH, ionic strength, and biomolecular interactions that can alter their structural integrity. These environmental factors often promote nanoparticle aggregation, reducing surface area and thereby diminishing antimicrobial activity. Aggregated nanoparticles may also elicit unintended biological responses or interfere with biodistribution. To mitigate these issues, researchers have explored encapsulating nanoparticles in hydrophilic polymers, functionalizing their surfaces with stabilizing agents, or designing core-shell architectures that protect the nanoparticle core while enhancing dispersion and targeting (Vasudevan *et al*., 2020).

The regulatory landscape surrounding nanomedicine remains complex and underdeveloped. Unlike conventional pharmaceuticals, nanoparticle-based therapies do not always conform to existing regulatory frameworks, leading to uncertainty in their clinical approval pathways. Clear guidelines regarding nanoparticle characterization, safety evaluation, manufacturing consistency, and environmental impact are still evolving. Furthermore, transitioning from laboratory research to clinical practice requires extensive validation through multi-phase preclinical and clinical trials (Autore *et al*., 2023). This translational gap presents logistical and financial challenges, particularly when nanoparticle synthesis methods lack scalability or when long-term safety data are limited. Collaborative efforts among researchers, industry, and regulatory agencies are vital to establishing harmonized protocols that facilitate the responsible development of nanotherapeutics (Lee *et al*., 2020).

An emerging area of concern is the potential for pathogens to develop resistance to nanoparticles. Although metal nanoparticles possess multifaceted mechanisms of action-such as membrane disruption, oxidative stress induction, and DNA interference there is growing evidence that continuous exposure to sub-lethal concentrations may lead to adaptive responses in bacteria (Lee *et al*., 2024). These adaptations may include efflux pump activation, biofilm enhancement, or changes in cell wall permeability. While the risk of resistance to nanoparticles is generally considered lower than with traditional antibiotics, it remains imperative to monitor resistance patterns over time. Integrating resistance surveillance into nanoparticle efficacy studies will help in understanding microbial evolution and guiding the design of next-generation materials that minimize the risk of resistance development (Orhan *et al*., 2024).

While nanoparticle-based strategies offer innovative and effective avenues for the treatment and prevention of urinary tract infections, their successful clinical adoption requires a careful and holistic approach. Addressing toxicity concerns, ensuring nanoparticle stability, navigating regulatory frameworks, and monitoring potential resistance are all crucial steps toward realizing the full potential of nanomedicine in UTI management. Sustained interdisciplinary research and transparent regulatory collaboration will play a pivotal role in overcoming these challenges and advancing safe, effective, and clinically viable nanotechnologies.

Future Directions

The future of Urinary Tract Infection (UTI) management is set to be transformed by the evolving field of nanotechnology, offering a new arsenal of tools that go beyond the limitations of conventional antimicrobial therapies. Ongoing innovations are poised to enhance therapeutic precision, reduce side effects, and overcome emerging antibiotic resistance-all while integrating seamlessly with existing treatment frameworks. Several promising avenues of research and development are now converging to shape the next generation of UTI diagnostics and therapeutics (Mancuso *et al*., 2023).

One key area of advancement is the use of ligand-conjugated nanoparticles for targeted drug delivery. These nanosystems are engineered to recognize specific surface markers on uropathogens, such as *Escherichia coli* or *Klebsiella pneumoniae*, via ligands like antibodies, peptides, or aptamers. Once bound to their bacterial targets, these nanoparticles release their antimicrobial payload directly at the site of infection, significantly enhancing therapeutic efficacy while minimizing systemic exposure. This precision-targeted approach not only reduces off-target toxicity but also allows for lower dosages of antimicrobial agents, thereby mitigating the risk of adverse effects and resistance development. Ongoing research is focused on identifying and optimizing ligand-receptor interactions specific to UTI pathogens to maximize this delivery efficiency (Rijk *et al*., 2024).

Another promising development is the creation of smart and stimuli-responsive nanomaterials that dynamically respond to

the local micro-environment within the urinary tract. These "intelligent" delivery systems can be designed to activate in response to pH shifts, temperature changes, or enzymatic activity-conditions commonly altered in infected tissues. Such responsiveness ensures that the release of therapeutic agents occurs only under infection-specific circumstances, thereby preserving healthy tissue and enhancing drug utilization efficiency (Werneburg and G. T., 2022). Additionally, some of these systems are being engineered with dual functionality, allowing them to serve not only as therapeutic agents but also as biosensors capable of detecting bacterial presence and monitoring infection status in real-time. This convergence of treatment and diagnostics (theranostics) offers new dimensions in personalized medicine for UTI management (Jabeen *et al.*, 2025).

As these technologies mature, clinical translation will be essential to bring nanotechnology-based treatments from bench to bedside. Future clinical trials must be designed to evaluate the safety, pharmacokinetics, and therapeutic outcomes of nanoparticle formulations in diverse patient populations. Particular attention will be needed to assess biocompatibility, potential immunogenicity, and long-term safety (Durrani *et al.*, 2023). Furthermore, regulatory frameworks governing nanomedicine are still evolving and will require refinement to address the unique challenges posed by nanoparticle behavior, characterization, and manufacturing. Collaborative efforts between regulatory agencies, research institutions, and pharmaceutical companies will be critical to defining standardized protocols and accelerating the approval of these novel therapeutics.

Another important direction involves the integration of nanotechnology-based strategies with conventional UTI treatment protocols. Nanoparticles can be used to complement traditional antibiotics, potentially enhancing antimicrobial action through synergistic effects. This integrated approach could help overcome resistant infections by simultaneously disrupting bacterial membranes, delivering antibiotics intracellularly, and modulating host responses (Chen *et al.*, 2022). Moreover, a holistic approach to UTI prevention and management should be adopted-one that incorporates nanotechnology alongside behavioral and dietary interventions, such as increased hydration, proper hygiene, and the use of cranberry-derived compounds. These complementary strategies can help reduce recurrence rates and improve overall urinary health (Akrah and Hessling, 2024).

In conclusion, the future of UTI management lies in the intelligent design and clinical integration of nanotechnology-based systems. Targeted ligand-conjugated nanoparticles, stimuli-responsive nanomaterials, and combination therapies represent a new frontier in personalized infection control. To fully realize their potential, interdisciplinary research, robust clinical validation, and well-defined regulatory pathways must align. With sustained innovation and collaboration, nanotechnology is poised to revolutionize how urinary tract infections are detected, treated, and prevented (Ioannou and Baliou, 2024).

CONCLUSION

This review has provided a comprehensive overview of the current landscape and emerging opportunities in the use of metal nanoparticles and nanocomposites for the management of Urinary Tract Infections (UTIs). Key findings from recent *in vitro* and *in vivo* studies demonstrate that nanomaterials such as silver, zinc oxide, copper oxide, selenium, and iron oxide nanoparticles exhibit potent antimicrobial activity against a broad spectrum of UTI pathogens. These nanoparticles disrupt bacterial membranes, generate reactive oxygen species, and release metal ions, making them effective not only against planktonic bacteria but also in eradicating biofilms, a major contributor to chronic and catheter-associated infections. The development of nanocomposites, particularly polymer-based and hydrogel-integrated systems, further enhances the antimicrobial performance and therapeutic stability of these formulations.

Application-based strategies, including nanoparticle-infused catheter coatings, intravesical therapies, smart controlled-release systems, and nanosensor-enabled diagnostics, offer targeted and patient-specific approaches that go beyond traditional antibiotic regimens. Moreover, future directions such as ligand-conjugated targeting systems and stimuli-responsive nanomaterials hold immense potential to transform infection control into a more precise, personalized, and minimally invasive paradigm.

Despite these advances, the safe and sustainable application of nanotechnology in UTI treatment remains a critical priority. Addressing toxicity concerns, improving biocompatibility, ensuring nanoparticle stability, and developing robust regulatory frameworks are essential to support the responsible clinical translation of these technologies. The risk of nanoparticle-induced toxicity or resistance development must be continuously evaluated through comprehensive preclinical and clinical assessments.

Therefore, nanotechnology represents a transformative frontier in the prevention, diagnosis, and treatment of UTIs. Its ability to enhance antimicrobial efficacy, overcome resistance, and enable site-specific drug delivery marks a significant shift from conventional therapeutic approaches. With continued interdisciplinary research, regulatory alignment, and a strong focus on safety and sustainability, nanotechnology-based solutions have the potential to revolutionize UTI management and improve patient outcomes on a global scale.

ACKNOWLEDGEMENT

We would like to thank Saveetha Institute of Medical and Technical Sciences for support.

ABBREVIATIONS

AMR: Antimicrobial resistance; **AMPs:** Antimicrobial peptides; **AgNPs:** Silver nanoparticles; **CAUTIs:** Catheter-associated urinary tract infections; **NCs:** Nanocomposites; **ESBL:** Extended-spectrum beta-lactamase; **Fe_2O_3 NPs:** Iron oxide nanoparticles; **H_2O_2:** Hydrogen peroxide; **MDR:** Multi-drug-resistant; MNPs: Metal nanoparticles; NPs: Nanoparticles; **O_2 :** Superoxide anions; **ROS:** Reactive oxygen species; **rUTIs:** Recurrent urinary tract infections; **SeNPs:** Selenium nanoparticles; **UPEC:** Uropathogenic *Escherichia coli*; **UTIs:** Urinary tract infections; **ZnO NPs:** Zinc oxide nanoparticles; **ZOI:** Zone of inhibition; **•OH:** Hydroxyl radicals.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

Mrs Bhakkia Rani Rajendran and Miss. Sulochana Govindharaj - Literature research, manuscript writing. Dr. Rajeshkumar Shanmugham Study Design, manuscript correction

SUMMARY

The expanding significance of nanotechnology in treating Urinary Tract Infections (UTIs), which are becoming more complex due to biofilm-associated recurrence and antibiotic resistance, is discussed in this review. It describes the antimicrobial mechanisms of metal-based nanoparticles, including metal ion release, membrane disruption, and the production of Reactive Oxygen Species (ROS). Examples of these nanoparticles include silver, copper, zinc oxide, selenium, and iron oxide. The review also emphasizes how combining nanoparticles with hydrogel-based or polymeric nanocomposites improves antibacterial activity and prevents the formation of biofilms. The study addresses novel approaches that are revolutionizing the treatment of UTIs, including nanosensor-assisted diagnostic tools, smart controlled-release drug delivery devices, and urinary catheters coated with nanoparticles. It also highlights persistent issues with the stability, toxicity, and regulatory approval of nanoparticles. Overall, the analysis come to the conclusion that although nanotechnology has revolutionary potential for UTI prevention, detection, and treatment, future research must concentrate on guaranteeing safety, biocompatibility, and long-term clinical translation.

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Cite this article: Rajendran BR, Shanmugam R, Govindharaj S. Recent Advances in Controlling of Urinary Tract Infecting Pathogens Using Metal Nanoparticles and Nanocomposites. Pharmacog Res. 2026;18(3):801-14.