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Review Article

Antibiotic-laden Nanoparticle Drug Delivery Systems for Enhanced Antimicrobial Activity and Reduced Multi-Drug Resistance

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Abstract

The rapid growth of multidrug-resistant bacteria presents a significant therapeutic challenge, necessitating the development of new antimicrobials and their combinations with nanoparticles (NPs). Nanoparticles have been used both independently and in combination to combat multidrug-resistant bacteria, offering new avenues through nanotechnology. The spread of antibiotic-resistant pathogenic bacteria has become a major global health issue. Traditional antibiotic treatments frequently contribute to the development of pathogen resistance, resulting in a reduced number of effective antimicrobials available for future use. The antibacterial activity was assessed through the minimum inhibitory concentration assay (MIC). Findings showed that substances including silver, gold, chitosan, and aminoglycosides entrapped silica networks alone had no or minimum effect on bacterial growth, but in combination, they greatly reduced bacterial growth. This review concludes the evolution of antimicrobial resistance, emphasizing the need for new synthetic or natural antibacterial agents in combination with NPs such as silver, gold, chitosan, and aminoglycosides entrapped silica networks providing insights into various medication strategies.

Keywords: Multidrug-resistant bacteria, nanoparticles, nanotechnology, minimum inhibitory concentration (MIC), multi-drug resistant (MDR), methicillin-resistant S. aureus (MRSA)

1. Introduction

The rapid global emergence of multi-drug-resistant bacteria is a significant challenge in contemporary medicine, necessitating innovative therapeutic strategies (Allahverdiyev et al. 2011, Fair and Tor 2014). Numerous infections caused by bacteria and a high frequency of microorganisms resistant to drugs reduce the efficacy of available therapies, raising the mortality rate (Fongang, Mbaveng, and Kuete 2023). According to a previous study by the European Antimicrobial Resistance Surveillance System, one-third of European countries had a Methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence rate to be more than 25% among bloodstream-isolated *Staphylococcus aureus* cases (Johnson 2011, Allahverdiyev et al. 2011). Growing resistance to antibiotics is one of the main concerns for public health, as well as a serious problem in Pakistan (Kumarasamy et al. 2010, Aslam et al. 2018). A study in Pakistan on MRSA isolates from skin and soft tissue samples has an antimicrobial resistance profile that shows high resistance rates to clindamycin, tetracycline, and cotrimoxazole (Idrees et al. 2009). One other study held in Karachi, Pakistan regarding vancomycin resistance emergence found that *Staphylococcus aureus* clinical isolates reflect the contemporary

pattern of high resistance to all the conventionally used antibiotics (Taj, Abdullah, and Kazmi 2010). One other study in Pakistan on MRSA isolates from skin and soft tissue samples had an antimicrobial resistance profile that showed significant resistance rates to clindamycin, tetracycline, and cotrimoxazole (Idrees et al. 2009). New approaches and enhancements to current techniques are desperately needed to address this issue. Metallic nanoparticles (NPs) are an efficient new way to overcome bacterial resistance because of their antibacterial properties (Rai et al. 2017, Gold et al. 2018, Correa et al. 2020).

2. Metallic Nanoparticles

The surface-to-volume ratio of metallic NPs is higher, and their size is lower, which increases their area of interaction with microorganisms. This characteristic increases chemical and biological activity, which gives NPs their strong antibacterial properties (Slavin et al. 2017, Correa et al. 2020). The ability of metallic NPs to target various bacterial structures is another significant characteristic. NPs can interfere with the permeability and respiration of cell membranes. Furthermore, NPs can effectively react with phosphorus-containing substances like DNA and sulfur-containing proteins to disrupt their functions, once they have penetrated bacterial cells (Rawashdeh and Haik 2009, Busi and Rajkumari 2019).

Metals with complex action mechanisms reduce the likelihood of bacteria becoming resistant to them. NPs are widely utilized in antibacterial activity has steadily increased in recent years. The most often utilized NPs in antimicrobial research are those made of silver, iron, titanium, copper, and zinc oxides (Correa et al. 2020, Yılmaz et al. 2023).

3. Challenges and Toxicity

Metallic NPs have remarkable antibacterial capabilities, but they also have several drawbacks. Certain mammalian cells have proven that nanoscale structures are harmful (Lewinski, Colvin, and Drezek 2008, Ivask et al. 2014, Bondarenko et al. 2013). Wang et al. examined the acute toxicity of oral administration of 5 g/kg body weight of nanoscale zinc powder in mice. Along with modest stomach irritation, they found abnormal lesions in the liver, kidneys, and cardiac tissue (Wang et al. 2006). In addition, Fe_2O_3 NPs disrupted blood coagulation parameters following intratracheal instillation and enhanced microvascular permeability and cell lysis in lung epitheliums (Kalan and Wright 2011, Areecheewakul 2021). Unlike larger particles, NPs can be taken up by cell nuclei and mitochondria. Once internalized by these organelles, these NPs may have the capacity to alter DNA (Singh et al. 2008, Sakhrani and Padh 2013, AshaRani et al. 2009). However, as a promising way to lessen the possible hazardous effects of NPs on mammalian cells, recent studies have looked into mixing nanoparticles with essential oils, antimicrobial peptides, and antibiotics. Owing to the reduced need for large dosages and the synergistic enhancement of their antibacterial activity, the co-administration of NPs and antibiotics can lessen the toxicity of both entities toward human cells. Among the research focused on investigating how metallic NPs and antibiotics work together, the most prevalent one involves the investigation of antibiotic interactions with silver nanoparticles (Abo-Shama et al. 2020, Shabatina, Vernaya, and Melnikov 2023).

4. Mechanism of Action

The only way to combat antibiotic resistance is to comprehend its mechanisms. Antibiotic resistance can arise from a variety of mechanisms, such as the antibiotic being ejected from the bacterial cell by efflux pumps, the antibiotic being broken down or modified by enzymes, or modifications to the antibiotic target that stop the antibiotic from attaching and losing its effectiveness. The mechanisms described suggest that different strategies need to be used. These strategies could

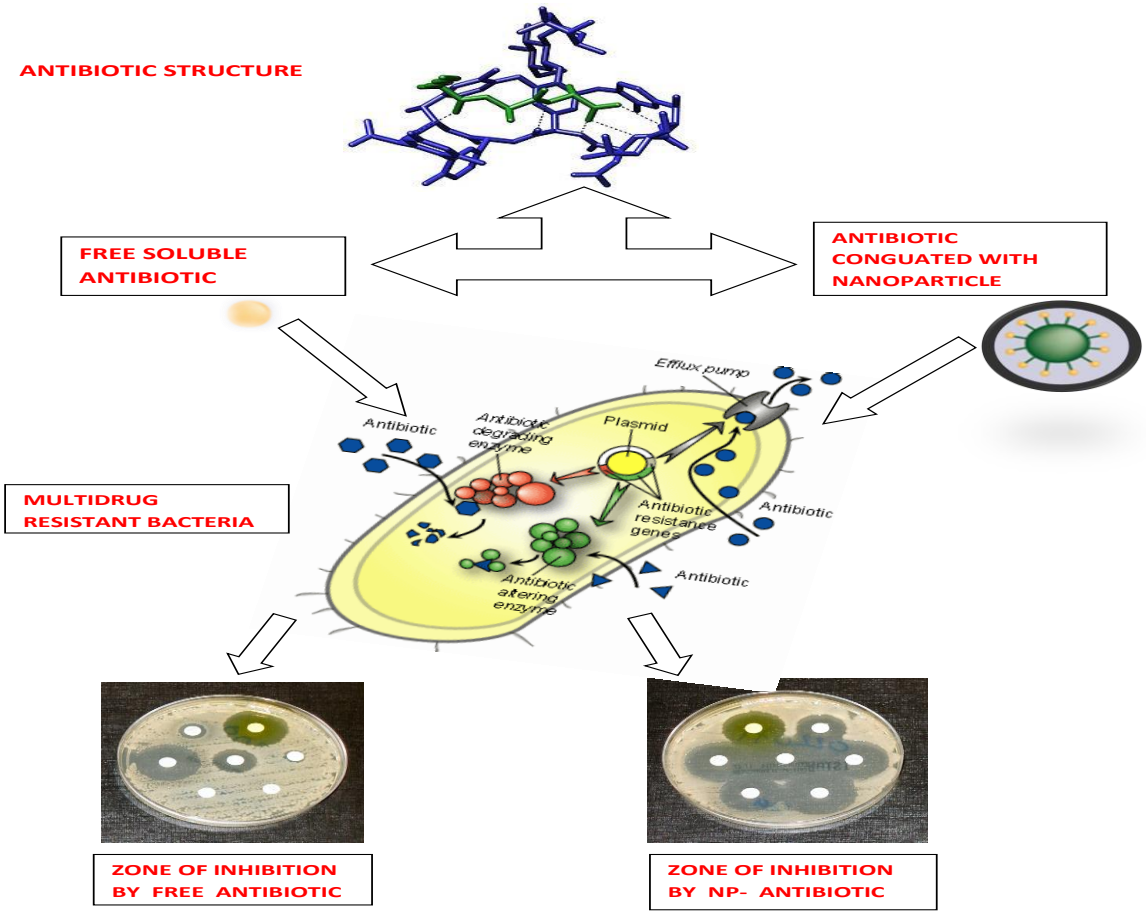

Figure 1: Visual illustration of the mechanism by which antibiotic-loaded nanoparticles exhibit synergistic antimicrobial effect.

include harnessing the combined effects of antibiotics and non-antibiotics to inhibit resistance enzymes that break down or alter antibiotics, preventing the expulsion of antibiotics from cells, or enhancing the ability of antibiotics to enter cells (Zhu et al. 2008). The zone of inhibition was high when antibiotic-laden nanoparticles were used against multi-drug-resistant bacteria as compared to free antibiotics as shown in Figure 1. Also illustrated in Fig. 1 is the mechanism by which antibiotic-laden nanoparticles exhibit synergistic antimicrobial effects.

5. Silver-laden Antibiotic

Numerous theories have been put forth to explain why silver nanoparticles inhibit a microorganism's activity. It is proposed that the primary component of silver's antibacterial action is its strong affinity for phosphorus and sulfur. Bacterial cell viability can be impacted by silver nanoparticles reacting with sulfur-containing amino acids, either inside or outside the cell membrane, due to a high concentration of sulfur-containing proteins on the membrane of bacteria. Additionally, it was proposed that the discharge of silver ions, specifically Ag+, from silver nanoparticles might react with proteins that contain sulfur to impair the activity of enzymes, or it could interact with phosphorus moieties in DNA to inactivate DNA replication (Gupta and Silver 1998),(Matsumura et al. 2003). The consensus is that Ag nanoparticles, which usually have diameters fewer than twenty nanometers, bind themselves to sulfur-containing proteins in bacterial cell membranes, increasing the

membrane's permeability and ultimately killing the bacterium (Morones et al. 2005).

Li et al. published one of the studies on this subject in which they examined the joint efficaciousness of amoxicillin and silver nanoparticles (AgNPs) against *E. Coli*. The minimal inhibitory concentration (MIC) of amoxicillin and silver nanoparticles, both separately and together, in the Luria-Bertani medium was ascertained by the authors. Findings showed that amoxicillin and AgNPs alone had no effect on bacterial growth, but in combination, both greatly reduced bacterial growth. MICs were 40 μg/ml for silver nanoparticles and 0.5 mg/ml for amoxicillin, respectively. On the other hand, a reduced concentration of both substances was needed in combination to provide the same level of growth inhibition (silver nanoparticles and amoxicillin 5 μg/ml, and 0.150 mg/ml, respectively). Multiple reasons for this synergistic action against both antibiotic-resistant and non-resistant bacteria were put out by the authors. Differences in the mode of action can account for the higher activity observed in resistant strains. When a bacterium develops resistance to one of the agents, a different agent destroys the microorganism (Li et al. 2005). A study showed that at extremely low concentrations (0.0002 mg per μL), AgNPs demonstrated stronger antibacterial efficacy than gentamicin against isolates of *Pseudomonas aeruginosa* and vancomycin against isolates of *S. aureus* and MRSA. It was possible to effectively isolate silver NPs from *Escherichia hermannii*, *Citrobacter sedlakii,* and *Pseudomonas putida*. Based on Transmission electron microscopy (TEM) studies, the AgNPs varied in size from 4 to 30 nm, contingent upon the type of isolate employed and the metabolites it produced. Out of the three isolates that were evaluated, the existence of minuscule (4–12 nm) and stable (zeta potential: −22 mV) AgNPs was responsible for their superior antibacterial efficacy. A Study revealed the best antimicrobial activity test against *K. pneumonia*, *S. epidermidis*, *S. aureus,* and *E. coli*. Meanwhile, isolate S11P showed the best antimicrobial activity only against *P. aeruginosa*. The antibacterial activity of AgNPs was shown to be either superior or equal to that of gentamicin against isolates of *P. aeruginosa,* and vancomycin against isolates of *S. aureus,* and MRSA. In addition, results showed a clear synergistic effect between AgNPs and tested antibiotics. These results suggest the possibility of the use of AgNPs and selected antibiotics combination to treat fastidious infections (Saeb et al. 2014). Strong antibacterial efficacy against bacterial infection is demonstrated by another work on the formation of non-toxic nanocomposite by reduction of silver nitrate in the presence of a cationic polymer. Through electrostatic interaction, these nanocomposites with a high concentration of positive charge facilitate their adsorption to bacterial membranes. Additionally, the produced nanocomposites have synergistic antibacterial activities and are capable of killing both Gram-positive and Gram-negative bacteria efficiently without causing resistance in the bacterial population (Prasad et al. 2017, Pachaiappan et al. 2021, Alavi and Rai 2019). TEM was used to observe morphological changes, and the results indicate that these nanocomposites have the potential to cause intracellular contents to seep out. An examination of the antimicrobial mechanism verifies that the breakdown of the bacterial membrane, followed by the internalization of the nanoparticles into the cell and the inhibition of intracellular enzyme activity fatally impacted the bacteria.

According to the results of this study, this new antimicrobial substance has the potential in treating other infectious diseases and aid wound recovery in diabetic rats. Moreover, It has good cytocompatibility (Mei et al. 2014). In a further investigation, Ag and Gold (Au) NPs were coupled with the antibiotic ceftriaxone. Atomic force microscopy and the agar well diffusion method were used to compare the conjugates' anti-*E. coli* activity to that of pure ceftriaxone and unconjugated NPs. Ceftriaxone's antibacterial

activity was roughly doubled upon conjugation to AgNPs, and almost six times upon conjugation to AuNPs. Additionally, conjugation seems to improve the pharmacokinetic profile of the antibiotic. Ag conjugates caused serious membrane damage, while Au conjugates induced morphological changes in the cell (Shah et al. 2014). In a study, leaf extracts from *Mentha asiatica* Boriss. (Lamiaceae) and *Ocimum basilicum* L. (Lamiaceae) was infused with AgNPs. AgNP production can be observed using UV-visible spectroscopy. X-ray diffraction (XRD) analysis of the formed silver nanoparticles revealed a structure. Scanning electron microscopy (SEM) was used to characterize the morphology of the nanoparticles. The synthesized nanoparticles were active against *S. aureus* and *E. coli*. This study provides an eco-friendly method for biogenic AgNP production (Ibrahim et al. 2014).

Another investigation involved functionalizing Au and AgNPs in one step using ampicillin, which is also utilized as a reducing agent to change Au^{3+} and Ag^{+} into Au and AgNPs, respectively. This procedure offers a fully green synthetic method by doing away with the need for additional chemical reduction agents. Spectroscopic and microscopic techniques were carried out to investigate the nanostructure, morphology, crystallinity, and reaction yield of the NPs. The sizes of 10-33 nm spherical and amorphous NPs were produced. With a MIC of 0.14–1.09 μ g/mL, the freshly produced NPs exhibit excellent antibacterial activity against *Streptococcus pyogenes* (Hur et al. 2014, Patil et al. 2023).

6. Au-laden Antibiotic

Au particles are specifically and widely used in organisms because of their biocompatibility. A study investigated the NPs combination of Bacteriocin/Au was clinically and biochemically safe. Probiotics were taken into consideration for the management of intestinal infection with parasites because of their secretory products, known as bacteriocins. This is the first investigation into the effectiveness of bacteriocin against intestinal microsporidiosis (Mossallam, Amer, and Diab 2014). Additionally, novel photo-thermal uses of Au nanostructures are thoroughly shown to fight bacterial infections, and some helpful recommendations are also covered to enhance photo-thermal technologies for useful applications (Guan et al. 2021, Zhang et al. 2022, Zhao, Tang, and Jiang 2022). In the last few years, there has been a lot of interest in inorganic NPs due to their drastically different physical, chemical, and biological properties from their bulk counterparts. Recent discoveries have shown that shape and size have a significant impact on the electromagnetic, optical, and catalytic capabilities of noble-metal NPs. This has spurred further investigation into the synthesis pathways that enable more precise control over shape and size. Additionally, light-absorbing AuNPs coated with certain antibodies have been employed to use lasers to photo-thermally kill *Staphylococcus aureus* (Bhattacharya and Mukherjee 2008, Mocan et al. 2017, Pissuwan et al. 2010). Numerous studies have been conducted on the potential of superparamagnetic iron oxide nanoparticles (SPIONs) and their derivatives, aminosilane and Au-coated, to serve as antibacterial medication carriers that can infiltrate bacterial cells and biofilm mass. *P. aeruginosa* growth is inhibited by Au-functionalized magnetic NPs. Hospitalized patients frequently get infections from *P. aeruginosa*, and a sizable portion of the strains that are currently isolated are resistant to conventional antibiotic treatment. This study demonstrated how three different kinds of SPIONs affected *P. aeruginosa* growth in a long-term bacterial culture. According to the results, the growth of *P. aeruginosa* in bacterial cultures was significantly inhibited by Au-functionalized NPs, whereas the greatest growth suppression (a 40% drop) was exhibited at the 48-hour mark. These findings offer compelling proof that Fe3O4@Au nanoparticles can significantly inhibit *P. aeruginosa* development and open up new research avenues

for investigating this nanomaterial's antibacterial properties (Daniel and Astruc 2004). An investigation to determine the effects of AuNPs and bacteriocin produced by *Lactobacillus acidophilus* CH1 bacteriocin was carried out in immunosuppressed mice; afterward, infectivity and intestinal spore waste of treated mice was evaluated. The anti-microsporidian effects of bacteriocin were found to be notably strong This effectiveness was increased when bacteriocins and AuNPs were combined since this resulted in a remarkably long-lasting decrease (94.26%) in fecal spore shedding one week after therapy was stopped. Furthermore, mice injected with bacteriocin/AuNPs showed the largest reduction (89.7%) in intestinal spore load, followed by the bacteriocin-inoculated group (73.5%). The vitality of the spores found in the stool of the bacteriocin/AuNPs group was 92.4%, whereas that of the bacteriocin group was 93.7% (Mossallam, Amer, and Diab 2014). The creation of therapeutically sound metallic NPs is a crucial advancement in the realm of nanotechnology. In the current investigation, *Lonicera japonica* Thunb. (Caprifoliaceae) flower extract was used to manufacture AuNPs. AuNPs were characterized using various techniques, like UV-visible absorption spectroscopy, FTIR, SEM, EDX, TEM, SAED, and XRD. The antimicrobial activity of these AuNPs was evaluated using Gram-positive (*S. aureus* and *B. subtilis*), Gram-negative (*E. coli*), and *C. albicans* and *S. cerevisiae*. The results showed that the combination of ampicillin with AuNPs resulted in better antimicrobial effects (Nagajyothi, Lee, and Sreekanth 2014). According to one research, Au-Pt bimetallic NPs synthesized without surface modification are powerful antibacterial reagents, but pure AuNPs or pure Pt nanoparticles show no antibiotic activity.

Antibiotics work by increasing the amounts of adenosine triphosphate (ATP) and dissipating membrane potential. Unlike most antibiotics, these bimetallic NPs do not generate reactive oxygen species, which makes them special. These bimetallic noble NPs are non-toxic to human cells, which may allow for the development of a new class of antibiotics (Zhao et al. 2014).

Another work used *E. coli* to produce AuNPs, and its goal was verified by DLS analysis, SEM, TEM, and UV-visible spectroscopy (Khademi Mazdeh et al. 2014). The efficacy of the streptomycin-conjugated AuNPs against *E. Coli*, *Clostridium perferingens*, and *C. botulinum* was assessed. The investigation produced 5–20 nm NPs from 5 mM HAuCl4. When antibiotics and NPs were combined, the MIC and minimum bactericidal concentration (MBC) of streptomycin against *E. coli* were significantly reduced. Additionally, this compound was able to overcome the inherent streptomycin resistance of *C. botulinum* and *C. perferingens'*. Compared to conventional techniques, biological synthesis is a more environment-friendly procedure (Khademi Mazdeh et al. 2014, Weeramantri 2017).

7. Chitosan-laden Antibiotic

An investigation evaluated the *in vitro* antibacterial efficacy of nano-conjugated vancomycin against strains of *S. aureus* that were either resistant (VRSA) or sensitive (VSSA) to the antibiotic. Vancomycin was delivered to bacterial cells using chitosan NPs that had been labeled with folic acid, acting as a Trojan horse. The disc agar diffusion test, MIC, MBC, tolerance, and lowest inhibitory concentration were employed to evaluate the antibacterial effectiveness of nano-conjugated vancomycin against VSSA and VRSA strains. Biofilm development and cell viability were evaluated as markers of pathogenicity. The cell wall thickness was investigated using TEM analysis to determine the potential antibacterial mechanism of nano-conjugated vancomycin. According to the findings, vancomycin is better transported across epithelial surfaces in nanosized vehicles. Moreover, tolerance values demonstrated the high efficacy and potent bactericidal impact of vancomycin loaded into nano conjugate against VRSA. These findings give

additional support for antimicrobial therapy methods in the treatment of staphylococcal pathogenesis and have significantly improved our comprehension of the molecular structure and function of nano-conjugated vancomycin (Chakraborty et al. 2012).

8. Silica-laden Antibiotic

Another study titled "Improved activity of aminoglycosides entrapped in silica networks against microbial strains isolated from otolaryngological infections" investigated the effectiveness of synthetic and natural zeolites as aminoglycoside antibiotic-carriers, using microbial strains isolated from otolaryngological infections through an adapted diffusion method.

The growth inhibition zone diameters by the antibiotics entrapped in the silica networks dramatically increased, indicating that both natural and synthetic zeolites were effective aminoglycoside carriers. They also demonstrated a potentiator effect on the activity of kanamycin and streptomycin, particularly against Gram-positive bacterial strains. These findings showed how useful silica networks are in finding novel approaches to increase bioavailability and reduce antibiotic consumption (Mitra et al. 2014, Chakraborty et al. 2010).

9. Conclusion

We can conclude that NPs based drug delivery systems present an effective approach to minimizing multi-drug resistance. The NPs not only improve the penetration and retention of antimicrobials at infection sites but also minimize the impact on healthy cells. These studies underscore the potential of NP-based drug delivery systems in addressing the burgeoning threat of antimicrobial resistance while boosting the effectiveness of current treatments.

These systems enhance the bioavailability and targeting precision of antimicrobial agents, leading to more efficient treatments. By employing NPs, antimicrobials can more effectively infiltrate bacterial cells and bypass resistance mechanisms.

10. Future Perspective

Current findings seem to cast a favorable light on the antibiotic-laden NP-drug delivery system for reducing antimicrobial resistance. Advances in nanotechnology are anticipated to result in more advanced targeting mechanisms, enabling the delivery of antimicrobial agents precisely to infection sites, thereby minimizing toxicity. Furthermore, the development of this system that responds to specific stimuli, such as pH or bacterial enzymes, will enable for controlled and timely release of drugs. The incorporation of NPs of Au, Ag, and chitosan as biodegradable and biocompatible materials will further enhance the safety and environmental sustainability of these systems. Antimicrobial pharmaceutical preparations in conjugation with NPs are set to revolutionize the therapy of bacterial infections, offering an effective means of tackling multi-drug resistance and improving the efficacy of existing antimicrobial therapies.

Conflict of Interest

The authors declare that they have no conflicts of interest to disclose.

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Study Approval

There are no animal/human subjects involved so, this study requires no institutional or ethical review board approval.

Consent Forms

NA.

Authors Contributions

TY conceptualized the study and wrote the final manuscript, MQ and MA helped with the

literature search analysis and writing the first draft, EJA, ZN, OI, and SGN did the literature search and review of the studies, and TY supervised the whole project and wrote the final manuscript.

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