Editorial

Antibiotic-silver Nanoconjugates: Effective Strategies to Combat the Threat of Antimicrobial Resistance

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Introduction

Currently, antimicrobial resistance has become a major threat worldwide [1], hindering the effective functioning of antibiotics. Overcoming this challenge requires increasing antibiotic doses and, consequently, increasing toxicity [2]. One of the researchers' new strategy is to produce silver-antibiotic nanoconjugates [3]. Drug nanoconjugation has provided promising solutions as an innovative approach to the challenges associated with the reduced effectiveness of common antibiotics in combating multidrug-resistant (MDR) pathogens. Metal/metal oxide nanoparticles (MNPs), due to their unique optical-physicochemical properties, have shown exceptional biological activity, especially in antimicrobial, anticancer, and tissue regeneration applications [4, 5]. In particular, the green synthesis of metal nanoparticles endows them with distinct structural and functional properties, such as enhanced biocompatibility, reduced toxicity, improved dispersion, greater colloidal stability in aqueous environments, and improved biological interactions, compared to chemically or physically synthesized nanoparticles. These properties are beneficial for subsequent biological performance [6]. The simultaneous interaction of the antimicrobial mechanisms of antibiotics and the antimicrobial pathways of silver nanoparticles is a key advantage of antibiotic-silver nanoconjugates, as it reduces the possibility of developing stable bacterial resistance through single-gene mutations or targeted modification [7]. The drug conjugation strategy has attracted much attention due to its potential benefits, such as targeted drug delivery, controlled drug loading and release, increased efficacy, drug stabilization, reduced toxicity and side effects, restoration of antibiotic sensitivity, increased solubility of effective but poorly water-soluble antibiotics, and increased bioavailability.

Halawani et al. aiming to address the problem of treating infectious diseases caused by MDR bacteria, synthesized silver nanoparticles using the Rosa damascene (RD) plant, functionalized with chitosan (CS), and conjugated with cefotaxime. The authors emphasized the efficiency and safety of the plant extract-AgNPs-CS carrier as a novel targeted drug delivery system and proposed this type of design— which is toxic to MDR bacteria but harmless to normal cells— as an ideal and effective strategy to combat epidemic diseases [8].

Keshavarz et al. demonstrated significant suppression of cell proliferation and induction of apoptosis pathways in prostate cancer cells using silver nanoparticles synthesized by the hydroalcoholic extract of *Vaccinium arctostaphylos* (VA) fruit, coated with alginate macromolecules, and conjugated with the drug docetaxel. The

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drug release kinetic profile revealed a controlled and sustained release mechanism for docetaxel, reaching peak release at 24 hours [9].

In the biosynthesis of silver-amphotericin B nanoconjugate by Ahmad et al. a covalent ester bond is formed by the interaction of the activated carboxylic -COOH functional group present in amphotericin B—activated by the molecule 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC)—with the hydroxyl -OH groups of biomolecules present in the aqueous extract of *Maytenus royleanus* (MR), which are attached to the surface of silver nanoparticles. The immobilization of amphotericin B on a nanosilver substrate minimizes the possibility of its self-assembly. This results in the drug load being depleted in a longer period of time, increasing the drug's effectiveness in binding to the target (ergosterol) and consequently reducing its toxicity. Additionally, the possibility of fungal resistance to amphotericin B is minimized [10].

Zhang et al. reported that green silver nanoparticles play an effective role as phosphoethanolamine transferases (PEATs) inhibitors in combination with colistin (Propolis-AgNPs@Colistin) for the treatment of PEAT-positive bacterial infections [11]. Specifically, Ag^{+} ions easily replaced the Zn(II) cofactor in the active site of the PEAT metalloenzyme, resulting in the addition of phosphoethanolamine to catalyzed lipid A, which reduced the electrostatic attraction between colistin and the bacterial outer membrane. This disruption was the breaking point of bacterial resistance, increased colistin sensitivity, and ultimately led to the death of resistant bacteria.

Khan et al. by conjugating Artemisinin with nanoparticles synthesized through mediation by Aloe vera, convincingly demonstrated greater accumulation of the drug inside aggressive and highly metastatic breast cancer MDA-MB-231 cells (increased bioavailability) [12]. We believe that the in-depth knowledge of antibiotic-silver nanoconjugate systems documented here will help design effective strategies to combat the threat of antimicrobial resistance.

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