

Synergistic Effects Between Metal Nanoparticles and Commercial Antimicrobial Agents: A Review

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ABSTRACT Nanotechnology has expanded into a broad range of clinical applications. In particular, metal nanoparticles (MNPs) display unique antimicrobial properties, a fundamental function of novel medical devices. Combining MNPs with commercial antimicrobial drugs (*e. g.*, antibiotics, antifungals and antivirals) may offer several opportunities to overcome some disadvantages of their individual use and enhance effectiveness. MNPs-conjugates display multiple advantages. As drug delivery systems, the conjugates can extend the circulation of the drugs in the body, facilitate intercellular targeting, improve drug stabilization, and possess superior delivery. Concomitantly, they reduce the required drug dose, minimize toxicity and broaden the

antimicrobial spectrum. In this work, the common strategies to combine MNPs with clinically used antimicrobial agents are underscored. Furthermore, a comprehensive survey about synergistic antimicrobial effects, mechanism of action and cytotoxicity is depicted.

1. Introduction

The emergence of infectious diseases due to new pathogens and multidrug-resistant (MDR) strains has been a global health threat over the last decades.¹ A wide range of microbes survive and thrive on living and non-living surfaces contributing to the development of infectious diseases outbreaks, high levels of healthcare-associated infections and an increase of MDR pathogens. Consequently, significant health and financial costs occur due to the slower patient treatments, increasing hospitalization times, disruption of daily activities, discomfort or even death.^{2,3} Despite promising studies in the development of novel antimicrobial drugs, this field has not been able to keep up with the rapid increase of infections caused by MDR pathogens.^{4,6} It is estimated that antibiotic resistance is causing 700,000 deaths annually worldwide. This number is expected to rise more than 10 million deaths per year by 2050.⁷ In addition, the effectiveness of conventional antimicrobial drugs is rapidly declining due to mass overconsumption and imprudent dosage. Governments were forced to launch propaganda to inform the mass population of adequate antibiotics consumption.⁸ MDR pathogens pose a particularly grievous threat to human health, and even more with the increasing number of immune-compromised individuals, ageing, transplant complications, and stress.^{9,10} In addition, the global pandemic of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) intensified the problem of MDR pathogens and the demand for more effective antimicrobial agents. Similarly to other viral infections, severely ill patients are at increased risk of secondary bacterial or fungal infections that

can be fatal.¹¹ The existing therapeutics are target selective, with specific mechanisms of action. Different drugs are combined to provide additional mechanisms of action and broad-spectrum activity. This approach commonly increases the dosage and the adverse side effects.¹² Thus, the World Health Organization (WHO) has launched an action plan to foment the discovery of effective and safe antimicrobial agents with multiple mechanisms of action.¹³ Moreover, strategies to decrease the risk of microorganisms colonization are taken into account to develop new materials that can kill or inhibit microbial growth and adhesion onto surfaces.¹⁴

Nanotechnology is changing the way healthcare solutions are developed and provided, offering innovative routes to address the progress in antimicrobial therapy, drug delivery and development of advanced materials.^{15,16} Metal nanoparticles (MNPs) have been widely applied and studied due to their unique properties: their small size and high surface-volume ratio, ability to act at the cellular level, improved solubility, surface adaptability and multifunctionality.¹⁷⁻²⁰ Despite their exceptional properties and wide range of applications, nanoparticles pose a risk of adverse health effects in humans. *In vitro* and *in vivo* studies have shown that MNPs can penetrate the cells leading to oxidative stress, inflammation, DNA damage and organ toxicity, limiting their application.²¹

Few MNPs have been approved for clinical use by U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), and very few are under clinical trials. The complexity of nanotechnology requires regulatory frameworks related to the inherent risks of nanoparticles (toxicity), effects of exposure and administration routes. The approved drugs are mainly used for anticancer therapy, iron-replacement therapy, antimicrobial agents and bone graft substitutes.²²⁻²⁶ It is imperative to study the pharmacokinetics of MNPs drugs using appropriate models to improve the translatability of MNPs to clinical practice. The MNPs should reach the target site undamaged, with high selectivity and reduced accumulation in non-targeted cells, tissues and organs. Optimal

therapeutic benefits can be obtained by functionalizing the nanoparticles with appropriate ligands or combining other drugs.²⁷⁻³⁰

Synergistic approaches combine two or more substances that together have superior efficacy than any of each substance considered individually. The conjugation of MNPs with other antimicrobial compounds may enhance their effectiveness. New approaches in the fight against pathogens may be explored, including the revival of old antibiotics, to overcome the current drug resistance emergency.^{31, 32} These NPs-conjugates may exhibit several advantages, such as i) multiple targets and mechanisms of action; ii) suppression of the emergence of resistant pathogens; iii) improve self-assembly into nanostructures for delivery systems; iv) facilitate the intracellular targeting; v) prolong the circulation and stabilization of drugs in the body's systems; vi) decrease the individual dosages that consequently minimize host toxicity and vii) increase the spectrum of antimicrobial coverage during therapies.^{12, 33} The drug combination is a common strategy in clinical practice, and its therapeutic success has been attained for acquired immunodeficiency syndrome (AIDS), cancer, cardiovascular disease and microbial infections.³⁴

The synergistic effect between MNPs and commercial antimicrobial drugs have been studied for several years. Nevertheless, a relevant increasing number of publications have occurred in the last five years. Most of the synergistic studies focus on silver nanoparticles (AgNPs). However, other MNPs were also reported, such as gold (Au), copper (Cu), copper oxide (CuO), copper sulfide (CuS), iron (Fe), iron oxide (Fe₃O₄/Fe₂O₃), zinc, zinc oxide (ZnO) and platinum (Pt). MNPs have been combined with several antibiotics, antifungals and antiviral agents (**Chart 1**). However, a high number of compounds and MNPs remain unexplored.

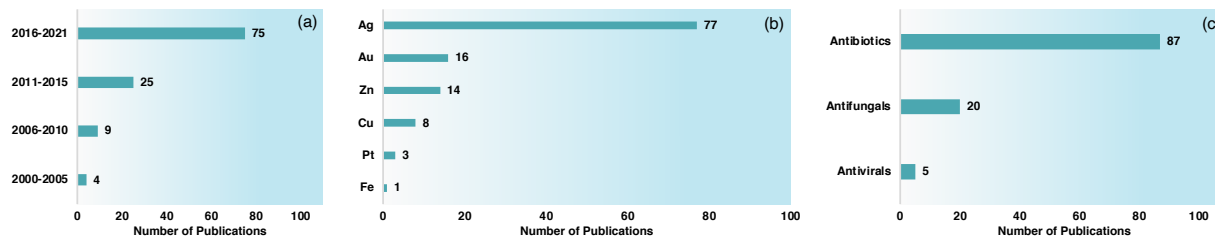


Chart 1. The number of (a) publications per year, (b) per type of MNPs, and (c) per conjugated drugs from 2000 until December 2021 in Google Scholar, Web of Science, PubMed, Scopus and Science Direct. The survey was conducted with a combination of keywords, using particular terms related to MNPs, combining agent and antimicrobial properties.

This review focus on the research works conjugating MNPs and commercial antimicrobial drugs such as antibiotics, antifungals and antivirals to obtain novel antimicrobial formulations. Therefore, conjugation of MNPs with other antimicrobial agents (*e.g.* disinfectants, antimicrobial peptides, novel organic molecules, essential oils) was not considered. The experimental methodologies to obtain the conjugates are described. The conjugates' antimicrobial efficacy, mechanism of action, and cytotoxicity are also depicted. Hence, this work envisages contributing to new advances on this topic and promoting the transfer of this knowledge and applications to clinical practice.

2. Metal nanoparticles as antimicrobial agents

MNPs research has increased due to their improved properties compared to bulk materials. They have allowed the development of novel drugs and materials by tailoring their size, morphology, distribution, and surface charge properties. However, MNPs toxicity to humans and the environment has been broadly reported. The main properties of MNPs responsible for their toxicological effect have been attributed to: i) size, NPs below 10 nm usually display high

antimicrobial activity but also high cytotoxicity due to their rapid diffusion into human cells and their ability to cross the blood-brain barrier (< 200 nm)³⁵⁻³⁷; ii) agglomeration, that contributes to the sedimentation process and reduce the diffusion of NPs, resulting in higher effective doses³⁸; and iii) surface charge, the charge of NPs present an essential role in regulating the protein binding to NPs, cellular uptake, oxidative stress, autophagy, inflammation and apoptosis (charged NPs showed to be more cytotoxic than neutral forms, and positively charged NPs were more cytotoxic than negative variants of similar size).^{39,40} Currently, MNPs can be designed to reduce their toxicity to humans.⁴¹ The size can be tailored for optimal efficacy, and capping agents can be used to prevent agglomeration, avoid undesirable nanoparticles oxidation and enhance ions release. Commonly used capping agents are oleic acid, polyacrylic acid, polyethylene glycol (PEG), polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP).⁴²⁻⁴⁵

Therefore, in this section is described the most important biomedical MNPs applied in antimicrobial formulations, which include: silver, gold, copper, iron, zinc, titanium dioxide (TiO₂), aluminium oxide (Al₂O₃), platinum and palladium (Pd) (**Scheme 1**). The most common experimental strategies used for their synthesis and surface functionalization are also depicted.

Overall, the application of MNPs in biomedicine presents several advantages and some limitations, particularly patients' toxicity. Numerous challenges encompass a broad spectrum of fields of knowledge, such as biological, chemical and material engineering. A comprehensive approach to convert all the research generated information into suitable clinical practices is highly demanding. Nevertheless, the conjugation of tailored nanoparticles with other materials/molecules is an unlimited exploration field that could provide exceptional biomedical applications.

Silver	Antimicrobial, drug deliver, anticancer, anti-angiogenic and biosensors ^{46, 47}
Gold	Drug delivery, catalyst for medical therapy, antimicrobial conjugations, anticancer, gene therapy and diagnostic ^{48, 49}
Copper and copper oxide	Antimicrobial and catalysis ^{50, 51}
Iron and iron oxide	Anticancer therapy, magnetic resonance imaging, targeted drug delivery and cell separation catalysis ⁵²⁻⁵⁴
Zinc oxide	Personal care products, coatings, drug delivery, anticancer and antimicrobial ^{55, 56}
Aluminum oxide	Drug delivery, biosensing, cancer therapy, antimicrobial, biomolecular preservation, immunotherapy ⁵⁷
Titanium oxide	Drug delivery, photodynamic therapy, cell imaging, biosensors, and genetic engineering, antimicrobial ^{58, 59}
Platinum	Biomedical devices, anticancer therapies, cardiovascular diseases, bioimaging, nanozymes, biosensors, antimicrobial ^{60, 61}
Palladium	Photothermal agents, photoacoustic agents, antimicrobial, anticancer, gene/drug carriers, prodrug activators and biosensors ^{62, 63}

Scheme 1. MNPs used in biomedical applications.

2.1 Silver Nanoparticles (AgNPs)

AgNPs are the most prevalent inorganic nanoparticles applied as antimicrobial agent. AgNPs have demonstrated high antimicrobial activity comparable to Ag ionic form. However, several concerns have emerged regarding their cytotoxicity. The toxicity mechanisms, long-term accumulation effects and dose-response relationship are still grievously unknown.⁶⁴

2.2 Gold Nanoparticles (AuNPs)

AuNPs are extremely valuable in developing antibacterial agents due to their low toxicity, high propensity for functionalization, eclectic effects, easy detection and photothermal activity. AuNPs per se possess very low antimicrobial activity, but numerous studies on the antimicrobial activity of AuNPs conjugated with small molecules, such as drugs, vaccines and antibodies, have been reported.⁶⁵⁻⁶⁷

2.3 Copper Nanoparticles (CuNPs)

CuNPs have also been widely researched due to their antimicrobial properties and higher biocompatibility. Copper, after silver, is one of the most commonly used nanomaterials due to its low cost and ready availability. Although its synthesis remains challenging due to the high oxidation proneness of copper. Copper is susceptible to air oxidation, and its oxidized forms are thermodynamically more stable.⁵⁰

2.4 Iron oxide Nanoparticles (Fe_xO_yNPs)

The FDA approved Fe₃O₄/Fe₂O₃NPs in clinical applications mainly due to their high versatility in surface modification and stability. Iron oxides are the preferable nanomaterials in medical sciences since they display marginal toxicity, good biocompatibility, and excellent physicochemical properties such as superparamagnetism and stability in aqueous solutions. Nevertheless, the antimicrobial properties can only be observed at relatively high concentrations. Their activity can be adjusted by changing the surface potential, surface functional groups and the iron oxidation state.^{53, 54, 68}

2.5 Zinc oxide Nanoparticles (ZnONPs)

ZnONPs are inexpensive, possess bactericidal properties and have high biocompatibility with human skin.⁶⁹ They have been presented as one of the most interesting and promising MNPs.^{55, 56}

2.6 Titanium oxide Nanoparticles (TiO₂NPs)

The antimicrobial activity of TiO₂NPs has been widely studied. It was found that the photocatalytic effect on TiO₂ allows the inactivation of microorganisms due to its strong generation of radical oxygen species. One limitation of TiO₂ is the activation mechanism. Photons with enough energy are required to activate the surface of these MNPs to promote the catalytic

processes. Thus, the incorporation of dopants has been a strategy to improve the antibacterial performance of TiO_2 .^{59, 70-72}

2.7 Aluminium oxide Nanoparticles (Al_2O_3 NPs)

Al_2O_3 NPs are low-cost, easy to handle and effective against pathogenic microorganisms, including MDR bacteria. Nonetheless, the neurotoxicity and blood toxicity of Al_2O_3 NPs represent a concerning limitation. Thus, novel engineering strategies are needed to improve Al_2O_3 NPs biocompatibility.^{57, 73}

2.7 Platinum Nanoparticles (PtNPs)

PtNPs promote bacterial growth inhibition by catalyzing the hyperproduction of adenosine triphosphate (ATP). Although their potential, the antimicrobial activity of PtNPs has been poorly studied. The PtNPs did not show any cytotoxicity, but further studies are still needed. The conjugation of PtNPs with other materials can be applied to develop novel applications that require control of bacterial growth.⁶⁰

2.7 Palladium Nanoparticles (PdNPs)

The potential of PdNPs as an antimicrobial agent has shown to be similar or superior to other MNPs and standard drugs (streptomycin and ampicillin) already in use.^{62, 63} New studies involving these nanostructures need to be carried out to understand better the antimicrobial effect, the mechanism of action and also possible toxic effects.

3. Metal nanoparticle synthesis

Generally, MNPs can be synthesized using two different approaches: i) Top-down, where the bulk material is reduced by sputtering, chemical etching, thermal ablation, and ball milling processes; ii) Bottom-up, where single atoms are accumulated via condensation, vapour

deposition, sol-gel process, spray pyrolysis, chemical or electrochemical deposition, aerosol methods or reduction processes (electrochemical, chemical, biogenic or photochemical reduction).⁷⁴ To improve MNPs stabilization and avoid aggregation, surface-stabilizing agents are commonly used. The synthesis process defines the physicochemical properties of nanoparticles, which governs their size, shape, surface charge and oxidation state.⁷⁵⁻⁷⁷ These properties will considerably influence the interactions between MNPs and conjugated agents and, consequently, their antimicrobial performance and cytotoxicity.

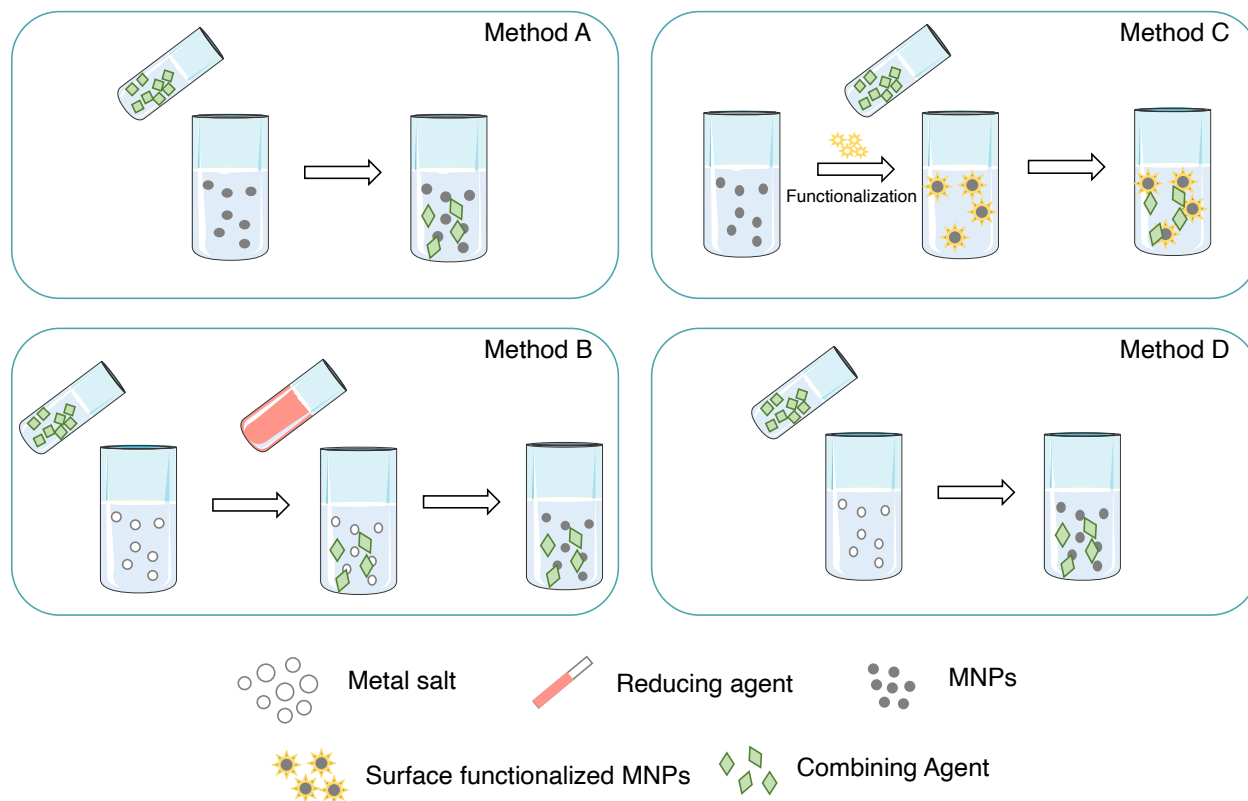
Chemical reduction and sol-gel have been the most employed methods for MNPs synthesis due to their simplicity. However, these protocols present high costs and are prone to generate toxic by-products.⁷⁸ The most common reducing agents in the chemical synthesis of MNPs may be replaced by biological materials such as bacteria, fungi or plant extracts. Nanoparticles synthesized from biological materials are known as biogenic nanoparticles. Their main advantages are cost-effectiveness and negligible environmental impact.⁷⁹ Nevertheless, biosynthesis of MNPs currently still possess a high polydisperse index and low reproducibility.⁸⁰

Therefore, methods for MNPs synthesis should be carefully pondered to design the MNPs properties according to the interactions required in the following steps.

4. Methods to combine MNPs and other antimicrobial agents

The preparation of MNPs conjugates with antimicrobial drugs (including antibiotics, antifungals and antivirals) is generally carried out via one of the following methods: method A – the MNPs synthesis and their posterior mixture with other agents' solutions; method B – MNPs synthesis in the presence of the combining agents; method C – MNPs synthesis, subsequent functionalization

and posterior conjugation step; and method D – MNPs synthesis using the conjugating agents also as reducing agents (**Scheme 2**).



Scheme 2. Common methods to conjugate MNPs and antibiotics, antifungals or antivirals.

In Method A, the MNPs are synthesized, and the solutions containing the conjugating agents are prepared separately. Subsequently, both solutions are mixed and characterized (**Scheme 2, method A**).

In the case of Method B, MNPs synthesis occurs in the presence of conjugating agents. The conjugating agent may or not act as a reducing agent. However, it is always associated with another reducing agent during the synthesis (**Scheme 2, method B**).

Method C conjugates MNPs and antimicrobial compounds through a three-step preparation: i) MNPs synthesis, ii) MNPs surface functionalization; iii) MNPs mixture with conjugating agents (**Scheme 2, method C**). In this case, the MNPs synthesis is an independent step that can be performed using any previously referred MNPs preparation methods. Afterwards, MNPs' surface is functionalized. The surface functionalization of metal and metal oxide nanoparticles has been used as a powerful tool to create bonds with organic molecules and biological cells, increasing the local concentration of MNPs in specific targets.⁶⁶ MNPs were mostly modified by thiols, disulfides, amines, nitriles, carboxylic acids and phosphines. Metal oxide nanoparticles were mainly functionalized by phosphonates or silanes. In addition, metal alkoxides, epoxides, metals or metalloids can cover the NPs surface to form an oxide film.^{81, 82} Finally, the MNPs are mixed with the conjugating agents in the desired proportion.

In the last approach, method D, the conjugation is obtained in one single step. The synthesis of MNPs unfolds using antimicrobials as reducing agents (**Scheme 2, method D**). In this case, the MNPs synthesis is performed using fewer chemicals, but it requires a long reaction time. Hur *et al.* (2014) described the functionalization of AuNPs and AgNPs with ampicillin, where ampicillin simultaneously acts as conjugating, stabilizing and reducing agent.⁸³

5. Therapeutic agents conjugated with MNPs and antimicrobial effect

Numerous works report the combination of MNPs and commercial antimicrobial drugs. Thus, this section was divided according to the drugs used: antibiotics, antifungals and antivirals.

The antimicrobial methods to evaluate the synergistic effects between MNPs and other agents alone and in combination are mainly based on *in vitro* tests by calculating the inhibition zones (ZoI), minimum inhibitory concentrations (MICs), the colonies reduction by plate counting

techniques or through optical density (OD) measurements. The checkerboard method is the most common and is based on the calculation of the fractional inhibitory concentration index (FIC) obtained by dividing the MIC value of the combined antimicrobial agent with the MIC of the antimicrobial agent per se. When the FIC value is ≤ 0.5 , the agents are considered synergic. FICs in the range of >0.5 to ≤ 1.0 are not synergistic or additive. FICs between >1.0 to ≤ 4.0 are negligible (indifferent) and FIC >4.0 are antagonistic.⁸⁴ This is a simple and effective procedure to assess synergistic effects. However, several literature references only depict MICs values and disregard FIC. Furthermore, other researchers estimate the synergism based on the obtained ZoI.

Unfortunately, the calculation of synergism is obtained using a wide range of different methods making it difficult to compare various reports adequately.³¹ It is imperative to reach a consensus concerning the method used to calculate synergism between MNPs and antimicrobial drugs. Therefore, the development of a standard is urgently needed.

5.1. Antibiotics

Antibiotic resistance is recognized as one of the most critical threats to human health. The generalized over-consumption of broad-spectrum antibiotics, such as glycylicyclines, oxazolidinones, carbapenems, and polymyxins, has increased during the last years. Efforts are needed to revitalize the antibiotic pipeline and develop novel antibiotics effective against antibiotic-resistance pathogens.⁸⁵ Antibiotic combinations are frequently used in clinical practice to circumvent antimicrobial resistance, though little is known about their impact on the human body.⁸⁶ Conjugating antibiotics with MNPs could re-establish antibiotic capability to destroy resistant bacteria. MNPs-antibiotics combinations have shown an increase in the concentration of antibiotics at their interaction site on bacteria.³¹ MNPs combination with antibiotics is the most

documented compared to other agents (87 studies in the total of 111 reports), and all classes of antibiotics may be found (**Table 1**).

Table 1. Antibiotics and corresponding classes used in synergistic studies with MNPs.

β-Lactams		Macrolides	Quinolones	Aminoglycosides
Amoxicillin	Ceftriaxone	Azithromycin	Ciprofloxacin	Amikacin
Amoxicillin/Clavulamic acid	Cefuroxime	Clindamycin	Enoxacin	Gentamicin
Ampicillin	Cephalexin	Erythromycin	Levofloxacin	Kanamycin
Aztreonam	Cephalothin	Nitrofurantoin	Nalidixic acid	Neomycin
Biapenem	Cephazolin	Rifampicin	Ofloxacin	Streptomycin
Carbenicillin	Feropenem	Oleandomycin	Oxolinic acid	
Cefaclor	Imipenem	Glycopeptides	Sulfonamides	Others
Cefazolin	Meropenem	Norvancomycin	Co-trimoxazole	Bacitracin
Cefepime	Methicillin	Teicoplanin	Trimethoprim	Chloramphenicol
Cefoperazone	Oxacillin	Vancomycin	Sulfanilamide	Fosfomycin
Cefotaxime	Penicillin	Tetracyclines	Polymixins	Fusidic acid
Cefoxitin	Penicillin G	Doxycycline	Colistin	Lincomycin
Cefpodoxime	Piperacillin	Oxytetracycline	Polymyxin B	Novobiocin
Ceftazidime		Tetracycline		
		Tigecycline		

β-Lactams and aminoglycosides were the most common antibiotics used in synergistic tests (**Chart 2**). Studies with Gram-negative bacteria were the most prevalent (191 studies), encompassing *Escherichia coli* (88 studies), *Pseudomonas aeruginosa* (36 reports), *Salmonella Typhimurium* (13 studies) and *Klebsiella pneumoniae* (12 documents) (**Chart 3**). The

Gram-positive studies (107) were mainly focused on *Staphylococcus aureus* (73 studies), including multiresistant *S. aureus* (MRSA).

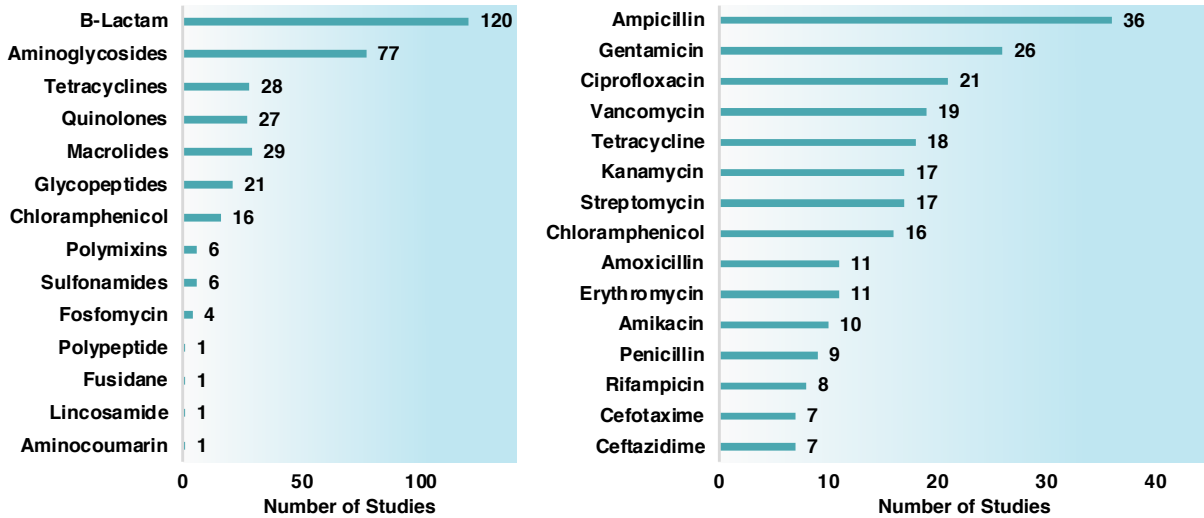


Chart 2. The number of studies organized on antibiotic classes (left graph) and antibiotic type (right graph) conjugated with MNPs.

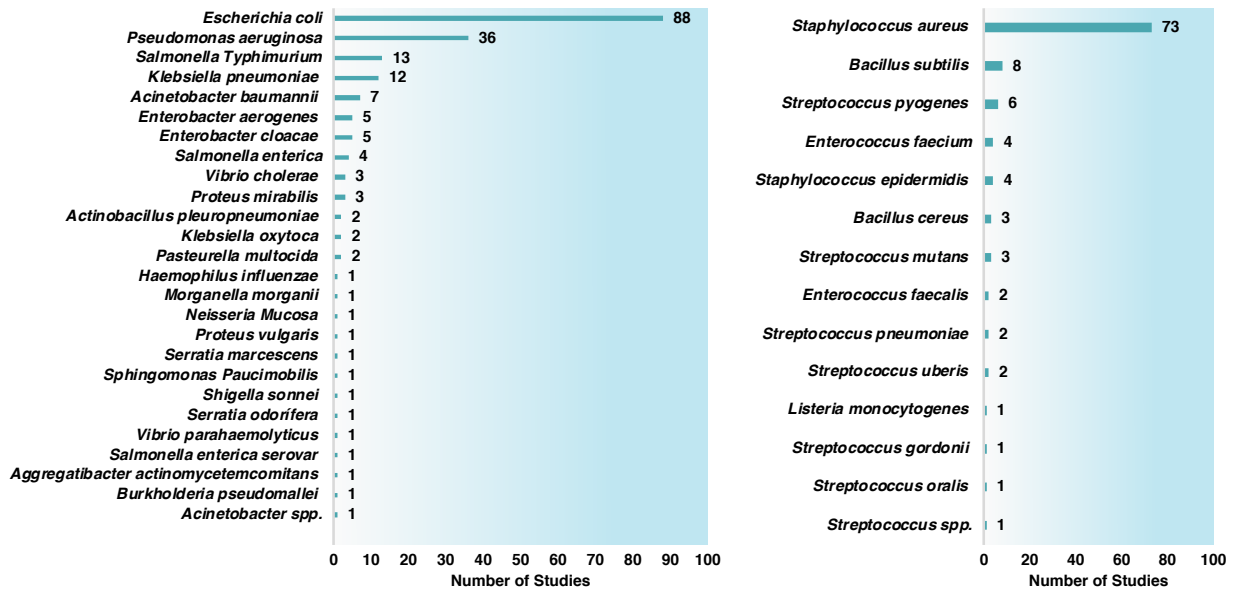


Chart 3. The number of studies involving antibiotics and MNPs against Gram-negative (left graph) and Gram-positive bacteria (right graph).

Regarding the MNPs conjugated to antibiotics, only AgNPs (61 studies), AuNPs (13 studies), ZnNPs or ZnONPs (11 studies), CuNPs or CuONPs (6 studies), PtNPs (2 studies) and FeNPs (1 study) were tested for synergistic activity. The referred research works in the following sections are presented according to conjugation method, MNPs synthesis method and MNPs type. Some examples are described for each type of MNPs, and a particular focus was given to the antimicrobial results and characterization methods when available.

5.1.1 Method A

Among the different strategies, method A (**Section 4, Scheme 2**) using MNPs synthesis and their posterior mixture with antibiotics solutions is the most used method to conjugate MNPs and antibiotics (**Table 2**).

Table 2. Synergic studies between MNPs and antibiotics obtained by the MNPs synthesis and their posterior combination with antibiotics – method A.

MNPs, size (nm)	MNs synthesis	Reducing Agent	Stabilizing Agent	Combined Antibiotics	Bacteria strains	Test method/Synergic results	Ref.
Ag, 3.0	Chemical	n.a.	n.a.	Ampicillin, chloramphenicol and kanamycin	<i>E. faecium</i> , <i>S. aureus</i> , <i>S. mutans</i> , <i>E. coli</i> and <i>P. aeruginosa</i>	FIC: <i>E. faecium</i> – ampicillin and chloramphenicol; <i>S. mutans</i> – ampicillin and kanamycin; <i>E. coli</i> – ampicillin and kanamycin; <i>P. aeruginosa</i> – chloramphenicol and kanamycin	87
Ag, 5.0-12.0	Chemical	Sodium borohydride and trisodium citrate	Trisodium citrate	Polymyxin B, rifampicin and tigecycline	Resistant <i>A. baumannii</i> strain	FIC: <i>A. baumannii</i> – polymyxin B and rifampicin	88
Ag, 8.0	Chemical	D-maltose and Sodium borohydride	Gelatin	Amoxycillin, penicillin G, gentamicin and colistin	<i>S. enterica</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>A. pleuropneumoniae</i> , <i>P. multocida</i> and <i>S. uberis</i>	FIC: <i>A. pleuropneumoniae</i> – penicillin G; <i>E. coli</i> – colistin; <i>S. aureus</i> – gentamicin	89

Ag, 8.6	Chemical	Gallic acid	Gallic acid	Ampicillin and amikacin	Clinical isolates (<i>E. faecium</i> , <i>S. aureus</i> , <i>A. baumannii</i> , <i>E. cloacae</i> , three different isolates of <i>E. coli</i> , <i>K. pneumoniae</i> , <i>M. morgannii</i> and <i>P. aeruginosa</i>)	FIC: <i>E. faecium</i> , <i>A. baumannii</i> , <i>K. pneumoniae</i> , <i>M. morgannii</i> and <i>P. aeruginosa</i> – ampicillin and amikacin; <i>S. aureus</i> , <i>E. coli</i> and <i>E. cloacae</i> , – amikacin	90
Ag, 10.0	Chemical	Sodium borohydride, trisodium citrate dihydrate and hydrazine	PVP and trisodium citrate dihydrate	Cephalexin nanoparticles (96 nm)	<i>S. aureus</i>	ZoI: <i>S. aureus</i> – cephalexin	91
Ag, 16.0	Chemical	Sodium borohydride and trisodium citrate dihydrate	PVP	Streptomycin, ampicillin and tetracycline	<i>E. coli</i> and <i>S. aureus</i>	ZoI: <i>E. coli</i> – streptomycin, ampicillin and tetracycline; <i>S. aureus</i> – streptomycin, ampicillin and tetracycline	92
Ag, 19.3	Chemical	Sodium borohydride and trisodium citrate dihydrate	SDS	Streptomycin, ampicillin and tetracycline	<i>E. coli</i> and <i>S. aureus</i>	ZoI: <i>E. coli</i> – streptomycin, ampicillin and tetracycline; <i>S. aureus</i> – streptomycin, ampicillin and tetracycline	92
Ag, 20.0	Chemical	Sodium citrate	Sodium citrate	Ampicillin	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> and <i>K. pneumoniae</i>	MIC: <i>E. coli</i> , <i>K. pneumoniae</i> and <i>P. aeruginosa</i> – ampicillin	93
Ag, 20.0	Chemical	Ascorbic acid	n.a.	Amoxicillin	<i>E. coli</i>	MIC: <i>E. coli</i> - amoxicillin	94
Ag, 20.0 nm	Chemical	Sodium borohydride	PVP	Vancomycin and amikacin	<i>S. aureus</i> and <i>E. coli</i>	ZoI: all combinations	95
Ag, 20.0 - 40.0 nm	Chemical	Tween 80	Tween 80	Gentamicin	<i>S. epidermidis</i>	FIC: synergism	96
Ag, 23.0	Chemical	Sodium citrate	Sodium citrate	Tetracycline, neomycin and penicillin G	<i>S. typhimurium</i>	MIC and inhibition (plate counting): <i>S. typhimurium</i> - tetracycline, neomycin and penicillin G	97
Ag, 25.0	Chemical	Ethylene glycol	PVP	Gentamicin	<i>E. coli</i> and <i>S. aureus</i>	FIC: <i>E. coli</i> and <i>S. aureus</i> – gentamicin	98

Ag, 25.0	Chemical	Sodium citrate	Sodium citrate	Vancomycin	<i>S. aureus</i> and <i>E. coli</i>	ZoI: all combinations	99
Ag, 26.0	Chemical	D-glucose	Starch	Erythromycin, ampicillin, chloramphenicol, cephalothin, clindamycin, tetracycline, gentamycin, amoxicillin, ciprofloxacin, ampicillin, cefpodoxime and cefuroxime	<i>S. aureus</i> , MRSA, <i>S. mutans</i> , <i>S. oralis</i> , <i>S. gordonii</i> , <i>E. faecalis</i> , <i>E. coli</i> , <i>A. actinomycetemcomitans</i> and <i>P. aeruginosa</i>	ZoI: <i>S. aureus</i> - erythromycin, clindamycin, tetracycline; <i>S. mutans</i> - gentamycin, amoxicillin, ciprofloxacin, cefpodoxime and cefuroxime; <i>S. gordonii</i> - erythromycin, cephalothin, clindamycin and tetracycline; <i>A. actinomycetemcomitans</i> - all combinations; <i>P. aeruginosa</i> - erythromycin, chloramphenicol and ciprofloxacin	100
Ag, 26.0	Chemical	D-maltose in alkaline media	Gelatin	Ampicillin, Ampicillin/Sulbactam, Cefazolin, Cefuroxime, Cefoxitin, Gentamicin, Co-trimoxazole, Colistin, Oxolinic acid, Ofloxacin, Tetracycline, Aztreonam, Piperacillin, Piperacillin/Tazobactam, Meropenem, Ceftazidime, Cefoperazone, Cefepime, Amikacin, Ciprofloxacin, Penicillin, Oxacillin, Chloramphenicol, Erythromycin, Clindamycin, Ciprofloxacin, Teicoplanin and Vancomycin	<i>E. coli</i> , <i>P. aeruginosa</i> and <i>S. aureus</i>	MIC: <i>E. coli</i> - ampicillin, ampicillin/sulbactam, aztreonam, cefazolin, cefoxitin, cefuroxime, co-trimoxazole, colistin, gentamicin, ofloxacin, oxolinic acid and tetracycline; <i>P. aeruginosa</i> - amikacin, aztreonam, cefepime, cefoperazone, ceftazidime, ciprofloxacin, colistin, gentamicin, meropenem, ofloxacin, piperacillin and piperacillin/tazobactam; <i>S. aureus</i> - ampicillin/sulbactam, chloramphenicol, ciprofloxacin, clindamycin, co-trimoxazole, erythromycin, gentamicin, oxacillin, penicillin, teicoplanin, tetracycline and vancomycin	101
Ag, 28.0	Chemical	D-maltose and Sodium borohydride	Gelatin	Amoxycillin, penicillin G, gentamicin and colistin	<i>S. enterica</i> , <i>S. aureus</i> , <i>E. coli</i> eae+, <i>A. pleuropneumoniae</i> , <i>P. multocida</i> and <i>S. uberis</i>	FIC: <i>A. pleuropneumoniae</i> - amoxycillin and gentamicin; <i>E. coli</i> - gentamicin; <i>S. aureus</i> - gentamicin	89
Ag, 28.0	Chemical	D-maltose	D-maltose	Cefotaxime, ceftazidime, meropenem, ciprofloxacin and gentamicin	Susceptible and resistant <i>E. coli</i> and <i>K. pneumoniae</i>	FIC: synergism in all resistant strains except to <i>K. pneumoniae</i> carbapenemase (additive effect)	102

Ag, 29.8	Chemical	Sodium citrate	Sodium citrate	Ampicillin, penicillin, enoxacin, kanamycin, neomycin and tetracycline	<i>S. typhimurium</i>	Colony counting: all combinations	103
Ag, 29.8	Chemical	Sodium citrate	Sodium citrate	Neomycin, kanamycin, enoxacin and tetracycline	Multidrug-resistant <i>S. typhimurium</i>	Inhibition (plate counting): <i>S. typhimurium</i> – enoxacin, kanamycin, neomycin and tetracycline	103
Ag, 38.3	Chemical	Sodium borohydride and trisodium citrate dihydrate	Trisodium citrate dihydrate	Streptomycin, ampicillin and tetracycline	<i>E. coli</i> and <i>S. aureus</i>	ZoI: <i>E. coli</i> – streptomycin, ampicillin and tetracycline; <i>S. aureus</i> – streptomycin, ampicillin and tetracycline	92
Ag, 70.0	Chemical	Trisodium citrate	Trisodium citrate	Vancomycin	<i>S. aureus</i> and <i>E. coli</i>	ZoI: all combinations	99
Au, 15.0 - 20.0	Chemical	Trisodium citrate	Trisodium citrate	Ciprofloxacin	n.a.	n.a.	104
CuO, 15.0	Chemical	Hydrazine	Polyethylene glycol	Meropenem and ciprofloxacin	Multidrug-Resistant <i>P. aeruginosa</i>	FIC: synergism using ciprofloxacin and meropenem	105
Fe and Cu, 6.0 - 9.0	Chemical	Hydrazine hydrate and sodium borohydride	n.a.	Gentamicin	<i>E. coli</i> , <i>P. aeruginosa</i> and <i>B. cereus</i>	ZoI: synergism	106
ZnO, 15.0	Chemical	Sol-gel with potassium hydroxide	n.a.	Cefotaxime, ampicillin, ceftriaxone, cefepime	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. paucimobilis</i> and <i>P. aeruginosa</i>	ZoI: <i>E. coli</i> – cephalexin, ampicillin, ceftriaxone and cefepime; <i>K. pneumoniae</i> – cephalexin, ceftriaxone and cefepime; <i>S. paucimobilis</i> – ampicillin and cefepime; <i>P. aeruginosa</i> – cephalexin, ampicillin and cefepime	107
ZnO, 35.0	Chemical	Polyethylene glycol	Polyethylene glycol	Meropenem and ciprofloxacin	Multidrug-Resistant <i>P. aeruginosa</i>	FIC: synergism with ciprofloxacin and meropenem	105
ZnO, 47.6	Chemical	Sodium hydroxide	Gelatin	Cefazolin	<i>S. aureus</i>	MIC: <i>S. aureus</i> - cefazolin	108
Mg-doped ZnO, 33.0	Chemical	PEG and sodium hydroxide	PEG	Chloramphenicol	<i>E. aerogenes</i> , <i>S. aureus</i> , <i>E. lentum</i> and <i>P. vulgaris</i>	ZoI: <i>E. aerogenes</i> , <i>S. aureus</i> , <i>E. lentum</i> and <i>P. vulgaris</i> – chloramphenicol	109
Ag-Au, 27.5	Chemical	Sodium hydroxide	Sodium acrylate	Doxycycline	<i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> and <i>M. luteus</i>	ZoI: <i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> and <i>M. luteus</i> – doxycycline	110

Cu-Zn, 21.0	Chemical	Triethylen e glycol	Triethylene glycol	Meropenem and ciprofloxacin	Multidrug- Resistant <i>P.</i> <i>aeruginosa</i>	FIC: all combinations	105
ZnO, 20.0 – 45.0	Mechano- chemical – milling process	n.a.	n.a.	Ciprofloxacin	<i>S. aureus</i> and <i>E.</i> <i>coli</i> clinical isolates	ZoI: <i>S. aureus</i> and <i>E. coli</i> – ciprofloxacin	111
Ag, 5.0- 20.0	Biogenic - bacteria	<i>Streptomy</i> <i>ces</i> calidiresis tents IF17 strain	Biomolecul es from actinobacter ial strains	Ampicillin, kanamycin and tetracycline	<i>E. coli</i> , <i>S. aureus</i> and <i>B. subtilis</i>	FIC: <i>E. coli</i> – tetracycline; <i>S.</i> <i>aureus</i> – ampicillin, kanamycin and tetracycline; <i>B. subtilis</i> – ampicillin, kanamycin and tetracycline	112
Ag, 5.0- 32.0	Biogenic - bacteria	Biomass from <i>Klebsiella</i> <i>pneumoni</i> <i>ae</i>	Protein caps from biomass	Penicillin, amoxicillin, erythromycin and vancomycin	Clinical isolates of <i>S. aureus</i> and <i>E. coli</i>	ZoI: <i>E. coli</i> – amoxicillin, erythromycin, penicillin and vancomycin; <i>S. aureus</i> – amoxicillin, erythromycin, penicillin and vancomycin	113
Ag, 5.0- 50.0	Biogenic - bacteria	<i>Streptomy</i> <i>ces</i> calidiresis tents IF11 strain	Biomolecul es from actinobacter ial strains	Ampicillin, kanamycin and tetracycline	<i>E. coli</i> , <i>S. aureus</i> and <i>B. subtilis</i>	FIC: <i>B. subtilis</i> – kanamycin	112
Ag, 17.0	Biogenic - bacteria	<i>Actinomy</i> <i>etes</i> strain	Protein caps from biomass	Ampicillin	<i>S. aureus</i> , <i>S.</i> <i>epidermidis</i> , <i>E.</i> <i>coli</i> , <i>P.</i> <i>aeruginosa</i> and <i>K. pneumoniae</i>	MIC and ZoI: <i>E. coli</i> , <i>K.</i> <i>pneumoniae</i> and <i>P. aeruginosa</i> – ampicillin	93
Ag, 20.0	Biogenic - bacteria	Biomass from <i>Klebsiella</i> <i>pneumoni</i> <i>ae</i>	Protein caps from biomass	Chloramphenico l, gentamicin and chloramphenico l/gentamicin	<i>E. faecalis</i>	ZoI: <i>E. faecalis</i> – chloramphenicol, chloramphenicol/ gentamicin and gentamicin	114
Ag, 35.0 - 60.0	Biogenic - bacteria	Silver Resistant Estuarine <i>P.</i> <i>aeruginos</i> <i>a</i> strain	Biomass from bacteria	Ampicillin and ciprofloxacin	Resistant <i>S.</i> <i>aureus</i> strain VN3 and Ciprofloxacin resistant <i>V.</i> <i>cholera</i> strain VN1	ZoI: all combinations	115
Ag-Au, 5.0 - 50.0	Biogenic - bacteria	<i>Pseudomo</i> <i>nas</i> <i>veronii</i> strain AS41G inhabiting <i>Annona</i> <i>squamosa</i> L.	Biomolecul es from <i>Pseudomon</i> <i>as veronii</i> strain AS41G	Bacitracin, chloramphenico l, erythromycin, gentamicin, kanamycin, streptomycin	<i>B. subtilis</i> , <i>E.</i> <i>coli</i> , <i>K.</i> <i>pneumoniae</i> and <i>S. aureus</i>	ZoI: all combinations	116
Ag, 5.0 - 30.0	Biogenic - fungal	Biomass from	Protein molecules	Imipenem, Gentamicin, Vancomycin	<i>E. coli</i> , <i>P.</i> <i>aeruginosa</i> and <i>E. faecalis</i> resistant to	ZoI: <i>A. baumannii</i> – ciprofloxacin; <i>Bacillus spp.</i> – ciprofloxacin, gentamicin, imipenem and vancomycin; <i>E.</i>	117

Aspergillus flavus from biomass and Ciprofloxacin trimethoprim, vancomycin, and ciprofloxacin; *S. aureus* resistant to trimethoprim and vancomycin; and *M. luteus* resistant to trimethoprim, gentamycin, and vancomycin. *A. baumannii* resistant to imipenem, trimethoprim, gentamycin, vancomycin, and *K. pneumoniae* and *Bacillus spp.* resistant to trimethoprim. faecalis – imipenem; *E. coli* – imipenem; *K. pneumoniae* – ciprofloxacin, gentamicin, imipenem and vancomycin; *M. luteus* – ciprofloxacin, gentamicin, imipenem and vancomycin; *P. aeruginosa* – ciprofloxacin, gentamicin, imipenem and vancomycin; *P. aeruginosa* – gentamicin, imipenem and vancomycin; *S. aureus* – gentamycin

Ag, 5.0 - 40.0	Biogenic - fungal	Biomass from <i>Trichoderma viride</i>	Protein molecules from biomass	Erythromycin, kanamycin, chloramphenicol and ampicillin	<i>S. typhi</i> , <i>E. coli</i> , <i>S. aureus</i> , and <i>M. luteus</i>	ZoI: <i>E. coli</i> – ampicillin, chloramphenicol, erythromycin and kanamycin; <i>M. luteus</i> – ampicillin, chloramphenicol and kanamycin; <i>S. typhi</i> – ampicillin, chloramphenicol, erythromycin and kanamycin; <i>S. aureus</i> – ampicillin, chloramphenicol, erythromycin and kanamycin;	118
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Ag, 8.0 - 12.0	Biogenic - fungal	Enzymes such as nitrate reductase and phytochelatin synthase from <i>Acinetobacter calcoaceticus</i>	Biomolecules secreted by the cells	Amikacin, Gentamicin, Kanamycin, Amoxicillin, Ampicillin, Penicillin, Ceftazidime, Ceftriaxone, Vancomycin, Ciprofloxacin, Doxycycline, Tetracycline, Chloramphenicol and Trimethoprim	<i>E. aerogenes</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. sonnie</i> , <i>S. typhimurium</i> , <i>S. aureus</i> , and <i>A. baumannii</i>	ZoI or MIC: <i>A. baumannii</i> – amikacin, amoxicillin, ampicillin, chloramphenicol, ciprofloxacin, doxycycline, gentamicin, tetracycline, trimethoprim and vancomycin; <i>E. aerogenes</i> – amikacin, amoxicillin, ampicillin, ceftriaxone, chloramphenicol, ciprofloxacin, doxycycline, gentamicin, kanamycin, penicillin, tetracycline, trimethoprim and vancomycin; <i>E. coli</i> – amikacin, amoxicillin, ampicillin, ceftazidime, ceftriaxone, chloramphenicol, ciprofloxacin, doxycycline, gentamicin, kanamycin, penicillin, tetracycline, trimethoprim and vancomycin; <i>P. aeruginosa</i> – amikacin, amoxicillin, ampicillin, ceftazidime, ceftriaxone, chloramphenicol, ciprofloxacin, doxycycline, gentamicin, kanamycin, penicillin, tetracycline, trimethoprim and	119
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vancomycin; *S. typhimurium* – amikacin, ampicillin, ceftazidime, ceftriaxone, chloramphenicol, ciprofloxacin, doxycycline, gentamicin, kanamycin, penicillin, tetracycline, trimethoprim and vancomycin; *S. sonnie* – amikacin, amoxicillin, ampicillin, ceftazidime, ceftriaxone, ciprofloxacin, chloramphenicol, ciprofloxacin, doxycycline, gentamicin, kanamycin, tetracycline, trimethoprim and vancomycin; *S. aureus* – amikacin, amoxicillin, ampicillin, ceftazidime, ceftriaxone, chloramphenicol, ciprofloxacin, doxycycline, gentamicin, kanamycin, penicillin, tetracycline, trimethoprim and vancomycin; *S. mutans* – amikacin, amoxicillin, ampicillin, ceftazidime, ceftriaxone, chloramphenicol, ciprofloxacin, doxycycline, kanamycin, penicillin, tetracycline, trimethoprim and vancomycin.

Ag, 30.0 - 70.0	Biogenic - fungal	Biomass from <i>Cryphonectria sp.</i>	n.a.	Streptomycin and amphotericin	<i>S. aureus</i> , <i>S. typhi</i> , and <i>E. coli</i>	ZoI: <i>S. aureus</i> , <i>S. typhi</i> , and <i>E. coli</i> - streptomycin	120
Ag, 66.7	Biogenic - fungal	Biomass from <i>Emericella nidulans</i>	Biomolecules from biomass	Amikacin, kanamycin, oxytetracycline, streptomycin	<i>E. coli</i> , <i>P. aeruginosa</i> and <i>S. aureus</i>	FIC: <i>E. coli</i> – amikacin and streptomycin	121
Ag, 81.1	Biogenic - fungal	Biomass from <i>Aspergillus flavus</i>	Biomolecules from biomass	Amikacin, kanamycin, oxytetracycline, streptomycin	<i>E. coli</i> , <i>P. aeruginosa</i> and <i>S. aureus</i>	FIC: <i>E. coli</i> – amikacin and streptomycin; <i>S. aureus</i> – kanamycin, oxytetracycline and streptomycin	121
Ag, 2.0	Biosynthesis - plant	<i>Dioscorea bulbifera</i> tuber extract	<i>Dioscorea bulbifera</i> tuber extract	Streptomycin, rifampicin, chloramphenicol, novobiocin and ampicillin	<i>E. coli</i> , <i>P. aeruginosa</i> and <i>S. aureus</i>	ZoI: all combinations	122
Ag, 2.0	Biosynthesis - plant	<i>Dioscorea bulbifera</i> tuber extract	<i>Dioscorea bulbifera</i> tuber extract	Streptomycin, rifampicin, chloramphenicol, novobiocin and ampicillin	<i>E. coli</i> , <i>P. aeruginosa</i> and <i>S. aureus</i>	ZoI: all combinations	122
Ag, 5.0 - 30.0	Biosynthesis - plant	Extract from	Protein molecules	Amikacin, gentamycin, kanamycin, streptomycin,	<i>A. baumannii</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>H. influenzae</i> , <i>K. pneumoniae</i> , <i>N.</i>	ZoI: <i>A. baumannii</i> – amoxicillin, ampicillin, cefotaxime, erythromycin, gentamycin, kanamycin, nalidixic acid,	123

<i>Dioscorea bulbifera</i>	from biomass	amoxicillin, ampicillin, penicillin, piperacillin, feropenem, ceftazidime, ceftriaxone, cefotaxime, polymyxin, vancomycin, erythromycin, nalidixic acid, rifampicin, tetracycline, doxycycline, chloramphenicol, nitrofurantoin and trimethoprim	<i>mucosa</i> , <i>P. mirabilis</i> , <i>P. aeruginosa</i> , <i>S. typhi</i> , <i>Serratia odorifera</i> , <i>V. parahaemolyticus</i> , <i>B. subtilis</i> , and <i>S. aureus</i>	nitrofurantoin, penicillin, piperacillin, rifampicin and rimethoprim; <i>B. subtilis</i> – ampicillin, cefotaxime, chloramphenicol, nalidixic acid, nitrofurantoin, penicillin, piperacillin, streptomycin, trimethoprim and vancomycin; <i>E. cloacae</i> – amikacin, amoxicillin, erythromycin, nalidixic acid and penicillin; <i>E. coli</i> – amikacin, erythromycin, kanamycin, nalidixic acid, polymyxin, streptomycin and trimethoprim; <i>H. influenzae</i> – cefotaxime, ceftriaxone, nitrofurantoin and trimethoprim; <i>K. pneumoniae</i> – amoxicillin, ampicillin, chloramphenicol, erythromycin, feropenem, nitrofurantoin, penicillin, rifampicin, trimethoprim and vancomycin; <i>N. mucosa</i> – amikacin, ampicillin, erythromycin, feropenem, gentamycin, nitrofurantoin, penicillin, polymyxin, tetracycline, trimethoprim and vancomycin; <i>P. mirabilis</i> – erythromycin, nalidixic acid and vancomycin; <i>P. aeruginosa</i> – amikacin, amoxicillin, ampicillin, chloramphenicol, doxycycline, erythromycin, feropenem, gentamycin, kanamycin, nalidixic acid, nitrofurantoin, penicillin, streptomycin, trimethoprim and vancomycin; <i>S. typhi</i> – amikacin, amoxicillin, ampicillin, cefotaxime, ceftriaxone, chloramphenicol, erythromycin, gentamycin, kanamycin, nalidixic acid, nitrofurantoin, penicillin, piperacillin, polymyxin, streptomycin, trimethoprim and vancomycin; <i>Serratia odorifera</i> – ceftazidime, erythromycin, nalidixic acid, nitrofurantoin, trimethoprim and vancomycin. <i>S. aureus</i> – amikacin, amoxicillin, ampicillin, ceftazidime, erythromycin, kanamycin, nalidixic acid, polymyxin, streptomycin and trimethoprim; <i>V. parahaemolyticus</i> – ampicillin, cefotaxime, ceftriaxone, kanamycin, nalidixic acid,
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						nitrofurantoin, polymyxin and trimethoprim	
Ag, 5.0 - 40.0	Biosynthesis - plant	Extract of <i>Argyrea nervosa</i>	Organic molecules from leaf extract	Vancomycin, streptomycin, tetracycline, gentamicin, Amoxicillin/clavulamic acid, erythromycin and ciprofloxacin	<i>S. aureus</i> and <i>E. coli</i>	ZoI: <i>S. aureus</i> - amoxicillin/clavulamic acid, ciprofloxacin, erythromycin, gentamicin, streptomycin, tetracycline and vancomycin; <i>E. coli</i> - amoxicillin/clavulamic acid, erythromycin, streptomycin, tetracycline and vancomycin	124
Ag, 5.8	Biosynthesis - plant	Gum kondagogu	Gum kondagogu	Streptomycin, gentamicin and ciprofloxacin	<i>S. aureus</i> , <i>S. aureus</i> , <i>E. coli</i> and <i>P. aeruginosa</i>	FIC: <i>S. aureus</i> - gentamicin and streptomycin; <i>S. aureus</i> - streptomycin; <i>E. coli</i> - streptomycin; <i>P. aeruginosa</i> - streptomycin	125
Ag, 7.4 - 18.3	Biosynthesis - plant	<i>Rosa damascenes</i> Extract	<i>Rosa damascenes</i> Extract	Cefotaxime	<i>E. coli</i> and MRSA	ZoI: all combinations	126
Ag, 15.0	Biosynthesis - plant	Extract from <i>Ulva fasciata</i>	n.a.	Azithromycin, gentamicin, oxacillin, cefotaxime, neomycin, ampicillin/sulbactam, cefuroxime, fosfomicin, chloramphenicol, oxytetracycline	<i>S. aureus</i> , <i>S. enterica</i> and <i>E. coli</i>	ZoI: <i>E. coli</i> - cefotaxime, cefuroxime, Fosfomicin, chloramphenicol, azithromycin and gentamicin <i>S. enterica</i> - azithromycin, gentamicin, oxacillin, cefotaxime, neomycin, ampicillin/sulbactam, cefuroxime, fosfomicin, chloramphenicol and oxytetracycline; <i>S. aureus</i> - azithromycin, oxacillin, cefotaxime, neomycin, ampicillin/sulbactam, cefuroxime, fosfomicin, chloramphenicol, oxytetracycline	127
Ag, 15.0 - 20.0	Biosynthesis - plant	<i>Eurotium cristatum</i> extract	<i>Eurotium cristatum</i> extract	Vancomycin, oleandomycin, ceftazidime, rifampicin, penicillin G, neomycin, cephalosporin, novobiocin, carbenicillin, lincomycin, tetracycline, and erythromycin	<i>C. albicans</i> , <i>P. aeruginosa</i> and <i>E. coli</i>	ZoI: all combinations	128
Ag, 20.0 - 30.0	Biosynthesis - plant	Extract from <i>Urtica dioica</i> Linn.	Extract from <i>Urtica dioica</i> Linn.	Streptomycin, amikacin, kanamycin, vancomycin, tetracycline, ampicillin, cefepime,	<i>B. cereus</i> , <i>S. epidermidis</i> , <i>S. aureus</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>S. typhimurium</i> , <i>K. pneumoniae</i>	ZoI: <i>B. cereus</i> - streptomycin, amikacin, kanamycin, vancomycin, tetracycline, ampicillin, cefepime, amoxicillin and cefotaxime; <i>S. epidermidis</i> - streptomycin, amikacin, kanamycin, tetracycline, ampicillin,	129

				amoxicillin, cefotaxime	and <i>marcescens</i>	<i>S. aureus</i> – streptomycin, amikacin, kanamycin, vancomycin, tetracycline, cefepime, amoxicillin and cefotaxime; <i>B. subtilis</i> – streptomycin, amikacin, kanamycin, vancomycin, tetracycline, ampicillin, cefepime, amoxicillin and cefotaxime; <i>E. coli</i> – streptomycin, amikacin, vancomycin, tetracycline, ampicillin, cefepime, amoxicillin and cefotaxime; <i>S.</i> <i>typhimurium</i> – streptomycin, amikacin, kanamycin, vancomycin, tetracycline, ampicillin, cefepime, amoxicillin and cefotaxime; <i>K.</i> <i>pneumoniae</i> – streptomycin, amikacin, kanamycin, vancomycin, tetracycline, ampicillin, cefepime, amoxicillin and cefotaxime; <i>S.</i> <i>marcescens</i> – streptomycin, kanamycin, tetracycline, ampicillin, amoxicillin and cefotaxime	
Ag, 45.3	Biosynthesis - plant	<i>Zea mays</i> extract	Extracts of corn leaves	Kanamycin and rifampicin	<i>B. cereus</i> , <i>L. monocytogenes</i> , <i>S. aureus</i> , <i>E. coli</i> and <i>S. Typhimurium</i>	ZoI: <i>B. cereus</i> , <i>E. coli</i> , <i>L. monocytogenes</i> , <i>S. Typhimurium</i> , <i>S. aureus</i> – kanamycin and rifampicin	130
Cu, 22.7	Biosynthesis - plant	Extracts from <i>Zingiber and Allium sp.</i>	Extracts from <i>Zingiber and Allium sp.</i>	Doxycycline	<i>P. aeruginosa</i> and <i>E. coli</i>	ZoI: synergism	131
CuO, 40.0 - 50.0	Biosynthesis - plant	Aqueous extract of <i>Tamarindus indica L.</i>	Aqueous extract of <i>Tamarindus indica L.</i>	Amoxiclav	<i>P. mirabilis</i> and <i>S. aureus</i>	FIC: synergism	132
ZnO, 66.0	Biosynthesis - plant	<i>Ficus carica</i> plant extract	Phytochemicals from plant extract	<i>E. coli</i> - Gentamicin, erythromycin and fosfomycin; <i>P. aeruginosa</i> - gentamicin, amikacin and ciprofloxacin; <i>S. aureus</i> - Fusidic acid, oxacillin and rifampicine; <i>Acinetobacter</i> - Tigecycline,	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Acinetobacter</i> and <i>P. mirabilis</i>	ZoI: all combinations	133

				Amikacin and rifampicine; <i>P. mirabilis</i> - gentamicin, erythromycin and fosfomicin			
ZnO, 187.0	Biosynthesis - plant	<i>Ulva fasciata</i> alga extract	n.a.	Azithromycin, gentamicin, oxacillin, Cefotaxime, neomycin, ampicillin/sulbactam, cefuroxime, fosfomicin, chloramphenicol, oxytetracycline	<i>S. aureus</i> , <i>S. enterica</i> subsp. <i>Bukuru</i> and <i>E. coli</i>	ZoI: <i>E. coli</i> - azithromycin, oxacillin, cefotaxime, ampicillin/sulbactam, cefuroxime, Fosfomicin and oxytetracycline; <i>S. enterica</i> - azithromycin, gentamicin, oxacillin, cefotaxime, neomycin, ampicillin/sulbactam, cefuroxime, fosfomicin, chloramphenicol and oxytetracycline; <i>S. aureus</i> - azithromycin, oxacillin, cefotaxime, neomycin, ampicillin/sulbactam, cefuroxime, fosfomicin, chloramphenicol and oxytetracycline	127
ZnO, 200.0	Biosynthesis - plant	<i>Pongamia pinnata</i> leaves extract	<i>Pongamia pinnata</i> leaves extract	Erythromycin	<i>P. aeruginosa</i>	ZoI: <i>P. aeruginosa</i> - erythromycin	134
Ag-Pt, 2.0	Biosynthesis - plant	<i>Dioscorea bulbifera</i> tuber extract	<i>Dioscorea bulbifera</i> tuber extract	Streptomycin, rifampicin, chloramphenicol, novobiocin and ampicillin	<i>E. coli</i> , <i>P. aeruginosa</i> and <i>S. aureus</i>	ZoI: all combinations excepting <i>P. aeruginosa</i> with novobiocin	122
Ag, 10.0 - 15.0	Commercial	n.a.	n.a.	Ampicillin, kanamycin, gentamycin and clindamycin	<i>A. baumannii</i>	Optical density: all combinations	135
Ag, 15.2	Commercial	n.a.	Starch	Ceftazidime, imipenem, meropenem and gentamicin sulfate	Clinical isolates (3) of <i>B. pseudomallei</i>	FIC: all combinations with the exception of one isolate with Ceftazidime and Imipenem	136
Ag, 35.0	Commercial	n.a.	PVP	Chloramphenicol, kanamycin, biapenem and aztreonam	<i>E. coli</i> , <i>S. enterica</i> serovar, <i>S. Typhimurium</i> , <i>S. aureus</i> and <i>B. subtilis</i>	FIC: <i>E. coli</i> - <i>S. typhimurium</i> and <i>S. aureus</i> - kanamycin	137
Ag, 10.0	n.a.	n.a.	PVP	Ampicillin	MRSA	Colony counting: synergism	138
ZnO, 17.1	Solventhermal	Glycerol	Ammonium citrate	Ciprofloxacin and ceftazidime	<i>A. baumannii</i>	ZoI: all combinations	139

In the research works combining AgNPs and antibiotics, AgNPs were mainly obtained by chemical or biochemical reduction with particle sizes varying between 2.0 and 81.0 nm. The AgNPs obtained using bacteria, fungi or plants presented a higher polydispersity index (PDI) when compared with the chemical synthesized nanoparticles. It should underscore the favorable antimicrobial properties achieved by combining AgNPs with commercial antibiotics, even against MDR strains.

Wan *et al.* (2016) reported a synergistic effect using AgNPs combined with the antibiotics polymixin B and rifampicin, and an additive effect using AgNPs-tigecycline. *In vivo* tests found that AgNPs–antibiotic combinations led to superior survival ratios in *A. baumannii*-infected mouse peritonitis.⁸⁸ Smekalova *et al.* (2015) performed 40 different combination tests, where 7 were synergistic, 17 additive and 16 indifferent. None of the tested combinations showed an antagonistic effect. The majority of synergistic effects were observed for combinations of AgNPs together with gentamicin. However, the highest enhancement of antibacterial activity was found with combined therapy with penicillin G against *A. pleuropneumoniae*. Moreover, *A. pleuropneumoniae* and *P. multocida*, which are resistant to amoxicillin, gentamicin and colistin, were sensitive to these antibiotics when combined with AgNPs.⁸⁹

Lopez-Carrizales *et al.* (2018) tested the activity of two classes of conventional antimicrobial agents (ampicillin and amikacin) alone and in combination with AgNPs against a set of ten MDR clinical isolates and two reference strains. The authors indicate that infections caused by MDR microorganisms could be treated using a synergistic combination of antimicrobial drugs and AgNPs. In this case, the combination of AgNPs with antibiotics promotes a decrease in the size of nanoparticles, observed in the transmission electron microscopy (TEM), from 8.57 ± 1.17 nm to 4.01 ± 0.80 nm using ampicillin, and 6.03 ± 0.87 nm using amikacin. The dynamic light scattering

(DLS) and zeta potential results showed more stable nanoparticles when combined with ampicillin, but less stable when the amikacin was used.⁹⁰

Salarian *et al.* (2017) showed the synergistic antibacterial properties of cephalexin NPs combined with AgNPs against *S. aureus*.⁹¹ Rogowska *et al.* (2017) assessed the antibacterial activity of biologically and chemical synthesized AgNPs functionalized with ampicillin against bacteria strains. The biosynthesized ampicillin-AgNPs showed a synergistic effect against *E. coli*, *K. pneumoniae* and *P. aeruginosa*. Whereas chemical synthesized AgNPs only exhibited synergism results against *K. pneumoniae* and *P. aeruginosa*. These results may be related to the differences in the stability of the nanoparticles when conjugated with ampicillin. Since biologically synthesized AgNPs were more stable than chemically generated AgNPs (zeta potential of -18.50 ± 0.99 mV and -11 ± 0.20 mV, respectively).⁹³ In another work, the authors combined chemical synthesized AgNPs with vancomycin and amikacin, demonstrating synergistic antimicrobial effect against *S. aureus* and *E. coli*. Here, the characterization of nanoparticles with and without antibiotics was performed by UV-vis spectroscopy comparing the corresponding surface plasmon resonance (SPR). The AgNPs alone showed a SPR at 431 nm, and a blue shift was observed by adding vancomycin (2 nm) and amikacin (15 nm). This effect can be attributed to the charge transfer between the antibiotics and PVP coated AgNPs. In addition, in the case of amikacin, it can also be due to the electronic transitions between different orbitals with the possibility of a nucleophilic substitution reaction between lone pair of electrons in the oxygen atom of PVP and the hydrogen atom of the amikacin amine group. Furthermore, electronic transitions may occur between bonding or non-bonding orbital to antibonding orbital.⁹⁵ In a similar work, Kaur *et al.* (2019) showed synergistic antimicrobial results combining citrate-capped AgNPs with vancomycin against *S. aureus* and *E. coli*. In this case, a red shift in SPR was observed in the UV-

vis spectra after the addition of vancomycin. The PDI and zeta potential showed an inferior PDI and superior stability of vancomycin-conjugated AgNPs. X-ray diffraction analysis (XRD) studies showed that the crystalline nature of AgNPs after antibiotic functionalization remains intact.⁹⁹

Mc Shan *et al.* (2015) suggest that the combination of the ineffective tetracycline or neomycin with AgNPs against *S. typhimurium* inhibits the growth of this bacterium. Nevertheless, the same was not verified for penicillin.⁹⁷ Wang *et al.* (2016) showed the enhanced antibacterial activities of AgNPs against three bacterial strains: *S. aureus*, *E. coli* and gentamicin-resistant *E. coli*. Indicating that gentamicin considerably promotes the dissolution of PVP-AgNPs, which not only increases the concentration of silver ions but also assists the attachment of PVP-AgNPs onto the surface of bacteria by mitigating the negative charge of the NPs.⁹⁸

Panáček *et al.* (2016) performed a systematic study to quantify the synergistic effects of antibiotics with different modes of action and different chemical structures combined with AgNPs against *E. coli*, *P. aeruginosa* and *S. aureus*. The researchers did not notice any trends for synergistic effects of antibiotics with different modes of action, which indicates a non-specific synergistic effect. Notably, a low amount of AgNPs was required for effective antibacterial action.¹⁰¹ Deng *et al.* (2016) combined citrate stabilized AgNPs with several antibiotics against non-resistant and MDR *S. typhimurium*, observing several synergistic combinations. In this work, a particular study was performed by Raman spectroscopy to verify the interaction between AgNPs and antibiotic molecules. The authors found that ampicillin and penicillin did not replace the stabilizing molecules used during synthesis. On the contrary, the antibiotics enoxacin, kanamycin, neomycin and tetracycline strongly interact with AgNPs, replacing the surface citrate molecules and forming antibiotic-AgNPs complexes. These antibiotics readily caused the agglomeration of AgNPs.¹⁰³

Just one work was found combining AuNPs and antibiotics using Method A. The work was developed by Tom *et al.* (2004), and the authors used ciprofloxacin to protect AuNPs, but no antimicrobial analysis were performed.¹⁰⁴

Bhande *et al.* (2012) demonstrated the potential of ZnONPs to act as the β -lactam antibiotics.¹⁰⁷ Rath *et al.* (2015) combined ZnONPs and cefazolin, showing a higher antibacterial activity.¹⁰⁸ Abo-Shama *et al.* (2020) tested the synergistic effect of antibiotics (azithromycin, oxacillin, cefotaxime, cefuroxime, fosfomycin and oxytetracycline) against *E. coli*. The results showed a significant increase in the presence of ZnONPs when compared to the antibiotic alone. They also tested the synergistic effect of antibiotics (azithromycin, cefotaxime, cefuroxime, fosfomycin, chloramphenicol and oxytetracycline) against *S. aureus*, which also showed significantly increased antimicrobial effect in the presence of ZnONPs.¹²⁷ Eleftheriadou *et al.* (2021) studied the potential of polyol-coated CuONPs and ZnONPs combined with the meropenem and ciprofloxacin as efflux pump inhibitors against MDR *P. aeruginosa*. The results demonstrated that all tested NPs act synergistically in the presence of the antibiotics, depending on the concentration.¹⁰⁵ Ghosh *et al.* (2021) showed synergistic results combining ZnO NPs with erythromycin against *P. aeruginosa*.¹⁴⁰ All these works confirm the synergistic effect of ZnONPs with different classes of antibiotics.

Cu or CuONPs have been revealed synergistic effects when combined with gentamicin, doxycycline and amoxicillin/clavulamic acid against *E. coli*, *P. aeruginosa*, *B. cereus*, *P. mirabilis* and *S. aureus*.^{106, 131, 132}

Vernaya *et al.* (2020) showed the efficacy of FeNPs as a promising precursor of targeted drug delivery systems. In this work, gentamycin was combined with chemical synthesized FeNPs.¹⁰⁶

Only three works were found displaying the development of bimetallic NPs and posterior conjugation with antibiotics, in particular: Ag-Au, Ag-Pt and Cu-Zn nanoparticles. Fakhri *et al.*

(2017) tested the synergistic antimicrobial activity of doxycycline conjugated bimetallic Ag-AuNPs against *P. aeruginosa*, *E. coli*, *S. aureus* and *M. luteus*, showing promising results for burn healing therapy.¹¹⁰ In more recent work, Cu-ZnNPs were, for the first time, tested by Eleftheriadou *et al.* (2021). The Cu-ZnNPs and meropenem combination resulted in an additive effect at 25 µg/mL and partially in a synergistic or additive effect at the two highest concentrations tested (50 and 100 µg/mL) against *P. aeruginosa*.¹⁰⁵ Lastly, Ranpariya *et al.* (2021), studied the bimetallic Ag-PtNPs combined with streptomycin, rifampicin, chloramphenicol, novobiocin and ampicillin against *E. coli*, *P. aeruginosa* and *S. aureus*. The inhibitory activity of Ag-PtNPs was more efficient against all pathogens than individual AgNPs or PtNPs. In the antimicrobial synergy tests, the activity of rifampicin and novobiocin combined with Ag-PtNPs showed a significant result against *S. aureus*.¹²² The bimetallic MNPs conjugated antibiotics showed interesting antimicrobial properties and may be a promising tool for developing novel agents.

5.1.2 Method B

In the case of method B, the MNPs synthesis were performed mostly using chemical methods, and in the presence of antibiotics (**Section 4, Scheme 2**). In this approach, the antibiotics may or not act as a reducing agent, but a stronger reducing agent is always applied (**Table 3**).

Table 3. Synergic studies between MNPs and antibiotics obtained by the MNPs synthesis in the presence of antibiotics – method B.

MNPs, size (nm)	MNs synthesis	Reducing Agent	Stabilizing Agent	Combined Antibiotics	Bacteria strains	Antimicrobial results	Ref.
Au, >14.0	Chemical	Sodium borohydride and ampicillin	Ampicillin	Ampicillin	<i>E. coli</i> , <i>M. luteus</i> and <i>S. aureus</i>	MIC: <i>E. coli</i> , <i>M. luteus</i> and <i>S. aureus</i>	¹⁴¹

						– ampicillin (slight synergism)	
Au, >14.0	Chemical	Sodium borohydride and streptomycin	Streptomycin	Streptomycin	<i>E. coli</i> , <i>M. luteus</i> and <i>S. aureus</i>	MIC: <i>E. coli</i> , <i>M. luteus</i> and <i>S. aureus</i> – streptomycin (significant synergism)	¹⁴¹
Au, >14.0	Chemical	Sodium borohydride and kanamycin	Kanamycin	Kanamycin	<i>E. coli</i> , <i>M. luteus</i> and <i>S. aureus</i>	MIC: <i>E. coli</i> , <i>M. luteus</i> and <i>S. aureus</i> – kanamycin (significant synergism)	¹⁴¹
Ag, 270.0	Chemical	Ammonia, polydopamine and vancomycin	Polydopamine	Vancomycin	<i>E. coli</i> and <i>S. aureus</i>	Colony counting: synergism	¹⁴²
Ag, 5.0 - 33.0	Chemical	Trisodium citrate and ampicillin or penicillin or vancomycin	Trisodium citrate and ampicillin or penicillin or vancomycin	Ampicillin, penicillin and vancomycin	<i>E. coli</i> , <i>K. pneumonia</i> , and <i>S. aureus</i>	FIC: <i>E. coli</i> – ampicillin and penicillin, <i>S. aureus</i> – penicillin and vancomycin; <i>K. pneumonia</i> – vancomycin	¹⁴³
Ag, 18.5	Chemical	Formic acid and Sulfanilamide	PVA and chitosan	Sulfanilamide	<i>E. coli</i> , <i>P. aeruginosa</i> and <i>S. aureus</i>	ZoI: <i>E. coli</i> , <i>P. aeruginosa</i> and <i>S. aureus</i> – sulfanilamide	¹⁴⁴
Ag, 5.0 - 33.0	Biosynthesis and Chemical	<i>Pyrenacantha grandiflora</i> Baill extract and ampicillin or penicillin or vancomycin	<i>Pyrenacantha grandiflora</i> Baill extract and ampicillin or penicillin or vancomycin	Ampicillin, penicillin and vancomycin	<i>E. coli</i> , <i>K. pneumonia</i> , and <i>S. aureus</i>	FIC: <i>E. coli</i> – vancomycin and penicillin; <i>K. pneumonia</i> – penicillin and ampicillin	¹⁴³

The antibiotics were conjugated with AgNPs or AuNPs by reducing the corresponding metal salts with sodium borohydride, tri-sodium citrate, ammonia, formic acid or plant extracts. The first demonstration of method B was performed by *Saha et al. (2007)*. The authors tested the synthesis of AuNPs using antibiotics (ampicillin, streptomycin and kanamycin) as reducing agents. However, the results showed that the used antibiotics did not exhibit sufficient reducing power to perform the redox reaction. The reaction time to obtain AuNPs took 4 h when ampicillin was used and 24 h with streptomycin or kanamycin. In addition to the extended reaction time, the obtained

antibiotic-conjugated AuNPs showed high agglomeration and quickly precipitated. Whereas the AuNPs produced using the combined reducing properties of both sodium borohydride and the antibiotics displayed superior stability. The SPR of antibiotics-conjugated AuNPs appeared in a more bluish region of UV-vis spectra, suggesting larger NPs as confirmed by TEM. Scanning electron microscopy (SEM) images showed different shapes of AuNPs using distinct antibiotics: cubic structure with ampicillin, rectangular rod-shaped with streptomycin and star-like structures with kanamycin. The AuNPs-conjugated antibiotics displayed superior bactericidal activity. The MIC values of the conjugates were determined against *E. coli*, *M. luteus* and *S. aureus*. Among them, streptomycin and kanamycin conjugates showed a significant reduction in MIC values. In contrast, AuNPs-ampicillin showed a slight decrease in the MIC value when compared to its free form.¹⁴¹ Ganesh et al. (2018), prepared AgNPs decorated with chitosan and polyvinyl alcohol (PVA) using formic acid as a reducing agent. The AgNPs were prepared in one solution containing sulphanylamide. The main objective of this experiment was to produce nanofibers with AgNPs incorporated. Thus, PVA was introduced to allow the electrospinning of the mixture. The antimicrobial tests and *in vivo* wound healing evaluation demonstrated superior and synergistic activity due to the combination of AgNPs and sulphanylamide.¹⁴⁴ Ma *et al.* (2020) developed an efficient nanohybrid using vancomycin-carrying polydopamine with AgNPs. Zeta potential, XRD and X-Ray photoelectron spectroscopy (XPS) analysis proved the successful AgNPs modification. In the XPS analysis, the survey spectra showed the presence of two specific peaks centered at 368.0 and 374.0 eV assigned to Ag 3d_{5/2} and Ag 3d_{3/2} electrons of Ag⁰, respectively. It proves the assembly of AgNPs (Ag⁰) with polydopamine. The synthesized hybrid showed synergistic antibacterial performance against both *S. aureus* and *E. coli* strains. The development of this hybrid allowed to reduce the drug dosage, decreasing the chance to develop drug resistance.¹⁴² In another

work, *Pyrenacantha grandiflora* tubers extracts were combined with ampicillin, penicillin, vancomycin and AgNPs. The antimicrobial activity was assessed against *E. coli*, *S. aureus* and *K. pneumoniae*. The overall results demonstrated that the conjugation of antibiotics with AgNPs are an effective option to improve the activity of antibiotics that have become less effective.¹⁴³

5.1.3 Method C

In the literature, few methods were found using method C (**Section 4, Scheme 2**). In this method, MNPs were synthesized, surfaces were functionalized and subsequently combined with antibiotics (**Table 4**).

Table 4. Synergic studies between MNPs and antibiotics obtained by MNPs synthesis, subsequent MNPs functionalization and combination of antibiotics – method C.

MNP s, size (nm)	MNs synthes is	Reducing Agent	Stabilizing Agent	Combined Antibiotics	MNPs Functionalization surface	Bacteria strains	Antimicrob ial results	Re f.
Ag, 4.0	Chemic al	Sodium borohydrid e	Trisodium citrate dihydrate	Ampicillin	Thioether group from ampicillin	<i>P. aeruginosa</i> , <i>E. aerogenes</i> , <i>E. coli</i> , <i>V. cholerae</i> , methicillin -resistant <i>S. aureus</i> and <i>E. coli</i>	MBC: <i>P. aeruginosa</i> , <i>E. aerogenes</i> , <i>E. coli</i> , <i>V. cholerae</i> , methicillin- resistant <i>S. aureus</i> and <i>E. coli</i> – ampicillin	145
Au, 4.0	Chemic al	Sodium borohydrid e	Trisodium citrate dihydrate	Ampicillin	Thioether group from ampicillin	<i>P. aeruginosa</i> , <i>E. aerogenes</i> , <i>E. coli</i> , <i>V. cholerae</i> , methicillin -resistant <i>S. aureus</i> and <i>E. coli</i>	MBC: <i>P. aeruginosa</i> , <i>E. aerogenes</i> , <i>E. coli</i> , <i>V. cholerae</i> , methicillin- resistant <i>S. aureus</i> and <i>E. coli</i> – ampicillin	145

Au, 4.0 - 5.0	Chemical	Sodium borohydride	n.a.	Vancomycin	Bis(vancomycin) cystamide	<i>E. faecium</i> , <i>E. faecalis</i> , <i>E. faecalis</i> resistant and <i>E. coli</i>	MIC: <i>E. faecium</i> , <i>E. faecalis</i> resistant and <i>E. coli</i> – vancomycin	146
Ag, 12.0	Chemical	Ethylene glycol	PVP	Ampicillin	Treatment with TEOS, reaction with APTES and Ampicillin addition	Susceptible and ampicillin-resistant <i>E. coli</i>	Inhibition (plate counting): the synergism was not assessed. The AgNPs-ampicillin conjugates showed a good antimicrobial effect for both strains with low cytotoxicity	147
Ag, 16.0	Chemical	Sodium borohydride	Mercaptoacetic acid	Norvancomycin	EDAC activated the reaction between carboxyl of mercaptoacetic acid and amide group of norvancomycin	<i>E. coli</i>	OD and inhibition (plate counting): <i>E. coli</i> – norvancomycin	148
Au, 2.0	Chemical	Sodium borohydride in the presence of 1-pentanethiol	Thiol groups	Ciprofloxacin and levofloxacin	Pentane-thiol capped AuNPs mixed with antibiotic	MDR <i>E. coli</i>	FIC: MDR <i>E. coli</i> – ciprofloxacin and levofloxacin	149
Au, 2.0	Chemical	Sodium borohydride in the presence of 1-pentanethiol	Thiol groups	Ciprofloxacin and levofloxacin	Synthesis of AuNPs, functionalization with pentane-thiol, mixture with antibiotics	MDR <i>E. coli</i>	FIC: MDR <i>E. coli</i> – ciprofloxacin and levofloxacin	149
ZnO, 20.0 - 24.0	Chemical	Sodium hydroxide	Starch	Ciprofloxacin	Amine functionalization of nanoparticles using 3-ethyl dimethylaminopropyl carbodiimide/N-hydroxysuccinimide (EDC/NHS)	<i>B. subtilis</i> , <i>Streptococcus spp.</i> and <i>E. coli</i>	ZoI: all combinations	150
Au, 15.0	Biogenic - fungal	Biomass of <i>Trichoderma</i>	Biomolecules from biomass	Vancomycin	Ionic interaction between the amino group of vancomycin	<i>E. coli</i> , <i>S. aureus</i> and vancomycin resistant	MIC: <i>E. coli</i> , <i>S. aureus</i> and vancomycin-resistant <i>S.</i>	151

<i>viride</i>	and negative surface charge of AuNPs	<i>S. aureus</i> strains	<i>aureus</i> – vancomycin
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Chemical and biogenic methods may be used for MNPs synthesis when following method C. The functionalization of MNPs surface is always a posterior step. AuNPs, AgNPs and ZnONPs were the only reported MNPs according to this method. AuNPs are the most frequent, probably due to their easy functionalization with thiol groups. Brown et al. (2012) synthesized AgNPs and AuNPs stabilized in citrate, and then, the NPs were functionalized with ampicillin. The thioether moiety present in the structure of ampicillin was used to attach the antibiotic to the AgNPs and AuNPs. Both nanoparticles functionalized with ampicillin exhibited active broad-spectrum bactericides against *Gram-negative* and *Gram-positive* bacteria. The conjugates are becoming potent bactericidal agents with unique properties that disrupt antibiotic resistance mechanisms of MDR strains.¹⁴⁵ Oliveira et al. (2016) functionalized chemical synthesized PVP-AgNPs with ampicillin using a multi-step method. First, a core-shell of silica in AgNPs was prepared by reaction with tetraethyl orthosilicate hydrolysis, forming the correspondent AgSiO₂NPs. Next, AgSiO₂NPs were coated with a thin silica/amine layer. In this step, an ethanol solution containing ammonia and AgSiO₂NPs reacted with tetraethyl orthosilicate (TEOS). The next step consisted in the reaction of NPs with 3-aminopropyltriethoxysilane (APTES). Finally, the NPs dispersion was mixed with an ampicillin solution in an acidic medium using 2-(N-Morpholino) ethanesulfonic acid.¹⁴⁷ Gu et al. (2003), demonstrated one synthetic route for formulating vancomycin-AuNPs with enhanced antibacterial activity. AuNPs reacted with bis(vancomycin) cystamide to form Au-S bonds that link vancomycin to AuNPs.¹⁴⁶ Fayaz et al. (2011) prepared vancomycin bound biogenic AuNPs by stirring the AuNPs dispersion and vancomycin for 24 h. The formulation was stable for at least 90 days. The vancomycin-AuNPs showed significant antibacterial activity

against *E. coli*, *S. aureus* susceptible and vancomycin-resistant strains. The vancomycin-AuNPs are shown to bind to transpeptidase instead of terminal peptides of the glycopeptide precursors on the cell surface of resistant *S. aureus*, inducing the lysis of the cell wall (**Figure 1**).¹⁵¹ The antibiotic-functionalized NPs were further characterized and the antimicrobial activity evaluated.

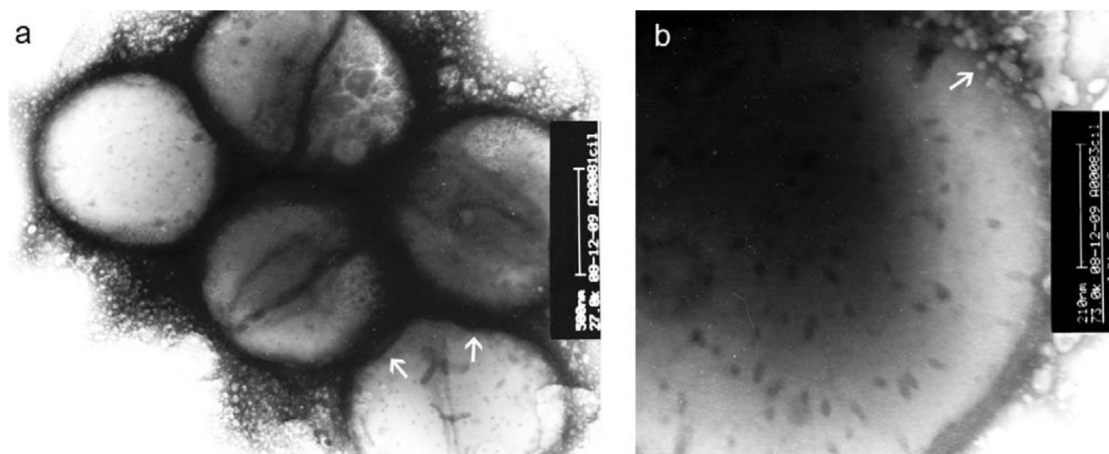


Figure 1. a) TEM images of vancomycin-resistant *S. aureus* cell treated with vancomycin-AuNPs conjugates; b) Expanded view of individual cell membrane of vancomycin-resistant *S. aureus* bacteria cell treated with vancomycin-AuNPs conjugates. Reproduced with permission from ref 151. Copyright 2011 Elsevier.

Gupta *et al.* (2017) performed a slightly different approach, where prior to the combination of antibiotics, the AuNPs were functionalized with thiol ligands. The chemical reduction of the gold salt was performed in the presence of 1-pentanethiol. The thiol protected AuNPs revealed to be highly stable due to the strong thiol-gold interaction. Next, the ligand functionalization of AuNPs core with hydrophobic ligands was done using a place-exchange method. The influence of the ligands onto NPs surface and their combination with fluoroquinolone antibiotics was studied. It demonstrated the synergistic antimicrobial therapy and decreased antibiotic dosage using

hydrophobically functionalized AuNPs and fluoroquinolone antibiotics to fight against MDR bacterial strains. The strategy shows the potential of using AuNPs to ‘revive’ ineffective antibiotics due to the development of resistance by bacteria.¹⁴⁹ QingShan *et al.* (2007) developed norvancomycin-capped AgNPs with notable antibacterial effects against *E. coli*. The antibiotic was grafted to the terminal carboxyl of the mercaptoacetic acid in AgNPs in the presence of N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDAC).¹⁴⁸ A report depicted this conjugation method with the antibiotic ciprofloxacin and amine-functionalized ZnONPs. The amine functionalization was obtained by a chemical process using 3-ethyldimethylaminopropyl carbodiimide (EDC) and N-hydroxysuccinimide (NHS). In antibacterial activity, synergistic effects were observed when ZnONPs were used in conjugation with antibiotics against all tested bacterial strains.¹⁵⁰

5.1.4 Method D

In the last approach, the synergistic effect was achieved by synthesizing MNPs using antibiotics as reducing agents, converging two steps in one (method D, **Table 5**).

Table 5. Synergic studies between MNPs and antibiotics obtained by MNPs synthesis using antibiotics as reducing agents – method D.

MNPs, size (nm)	MPS synthesis	Reducing Agent/antibiotic	Bacteria strains	Antimicrobial results	Ref.
Ag, 10.8 and 33.9	Chemical	Ampicillin	<i>S. aureus</i> , <i>S. pyogenes</i> , <i>P. aeruginosa</i> , <i>E. coli</i> , <i>S. typhimurium</i> , <i>Klebsiella</i> , <i>cloacae</i> and <i>S. pneumoniae</i>	MIC: the synergistic effect was not evaluated, the NPs without functionalization was not obtained, neither the MIC for antibiotics alone.	83
Ag, 44.1	Chemical	Ampicillin	<i>E. coli</i> , <i>S. aureus</i> , <i>ampicillin resistant E. coli</i> , <i>S. aureus</i> , <i>multi</i>	Zol: <i>E. coli</i> , <i>S. aureus</i> , <i>resistant E. coli</i> , <i>S. aureus</i> , <i>resistant P.</i>	152

			<i>drug resistant P. aeruginosa and K. pneumonia</i>	<i>aeruginosa and K. pneumonia – ampicillin</i>	
Au, 18.7	Chemical	Ampicillin	<i>S. aureus, S. pyogenes, P. aeruginosa, E. coli, typhimurium, Klebsiella, E. cloacae and S. pneumoniae</i>	MIC: the synergistic effect was not evaluated, the NPs without functionalization was not obtained, neither the MIC for antibiotics alone.	83
Au, 52.0 to 23.0	Chemical	Cefaclor	<i>S. aureus and E. coli</i>	MIC and Inhibition (plate counting): <i>E. coli</i> – cefaclor	153
CuS, 15.0	Chemical	Vancomycin	<i>E. faecium and E. faecalis</i>	Synergism not evaluated, enhanced bactericidal effect in antimicrobial phototherapy	154

Hur et al. (2014) described the functionalization of AuNPs and AgNPs with ampicillin, which acted as a reducing agent to convert gold and silver salts in the respective nanoparticles, minimizing the use of chemical agents during the synthetic route. Curiously, the newly-prepared NPs showed excellent antibacterial activity against *S. pyogenes*.⁸³ Khatoon et al. (2019), published the synthesis of AgNPs using ampicillin as a reducing agent. The PDI was found to be 0.32 and zeta potentials +33.42 mV, which indicate the long-term stability of Ampicillin-AgNPs suspension. The ampicillin content on conjugates was evaluated by thermogravimetric analysis (TGA), where 2.1% to 4.3% of weight loss between 30 and 200 °C was attributed to ampicillin on the surface of AgNPs. The antibacterial potential of ampicillin-AgNPs was studied against sensitive and drug-resistant bacteria. MIC values of ampicillin-AgNPs against six different bacterial strains were in the range of 3–28 µg mL⁻¹, which is much lower than the MIC of ampicillin alone (12–720 µg mL⁻¹) and chemically synthesized AgNPs (280–640 µg mL⁻¹). The results also indicated that bacterial strains do not show any resistance to ampicillin-AgNPs even after 15 successive cycles.¹⁵² Rai et al. (2010), reported a one-pot synthesis of spherical AuNPs capped with cefaclor without the use of other chemicals. The primary amine group in the cefaclor molecule acted as both the reducing and capping agent for AuNPs synthesis, leaving the β-lactam ring of

cefaclor available for its antimicrobial action. TEM images and DLS analysis showed the size of AuNPs from 52 ± 1.5 nm to 23 ± 2 nm with increasing temperature from 20 to 60 °C of the reaction solution. A red shift of 7 nm was observed in the SPR band centered at 528 nm when cefaclor was used, suggesting a small population of aggregated gold nanostructures in solution as also observed using TEM analysis. The TGA analysis showed three distinct weight losses at three different temperature regions indicating that cefaclor interacts with NPs by physical adsorption (weight loss in the lower temperature region), via rearrangement of bound cefaclor molecules (276 to 470 °C region) and by covalent bonds (515 to 660 °C). FTIR also confirmed the presence of cefaclor with the characteristic β -lactam ring vibrations at 1418, 1395 and 1357 cm^{-1} . The antimicrobial activity tests showed the growth inhibition of *E. coli*.¹⁵³ Covalently bonded method is preferred to simple physical adsorption due to the uncontrollable release of the drug from the nanoparticles of the latter. However, few reports were found using this strategy.¹⁵² Thus, novel experiments are needed to develop metal nanostructures combined with commercial antimicrobial agents to improve their bonding.

5.2. Antifungals

Invasive fungal infections have steadily increased over the last decades, and the mortality rates remains very high, especially in immunocompromised patients. It is estimated that more than 2 million people die annually of invasive fungal infections. This imperatively urges the identification of new classes of treatment options. For immunocompromised patients, the mortality is still very high for infections caused by *Candida albicans* (20–40%), *Candida neoformans* (20–70%) and *Aspergillus fumigatus* (50–90%), reaching a death rate of about 50%.^{155, 156} Recently, severe COVID-19 disease was correlated to an increase in pro-inflammatory markers, consequently

increasing susceptibility to bacterial and fungal infections such as mucormycosis, candidiasis (*Candida auris*), SARS-CoV-2-associated pulmonary aspergillosis, Pneumocystis pneumonia and Cryptococcal disease.¹⁵⁷ The antifungal agents available in current clinical treatments are very limited compared to antibacterial agents. They are not effective or safe due to the development of resistance and host toxicity.¹⁵⁸ Only five classes of antifungal drugs exist and include the azoles, polyenes, echinocandins, allylamines and antimetabolites. The available antifungal agents still exhibit several limitations in managing fungal infections. The emergence of drug-resistant fungi and the severe nephrotoxicity of some antifungals make the problem more and more serious.^{159, 160} The development of new antifungal agents is not matching the frequency of antifungal resistance appearance. The development of conjugate commercial antifungals has been attempted, but the trials have shown weak and sometimes contradictory results. Thus, more experiments and more specific recommendations for clinicians are needed.¹⁶¹ In the last years, few works have been published considering antifungal agents and MNPs (13 studies). Most of them used AgNPs and azole or polyene drugs. Fluconazole and amphotericin B were the most prevalent antifungal agents. The efficacy of antifungal drugs and MNPs combinations against *Candida albicans* (14 studies) was the most studied (**Chart 4**).

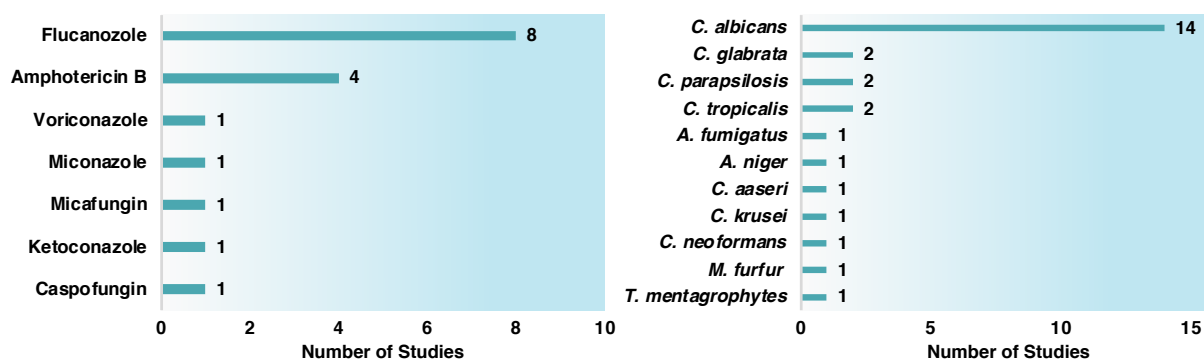


Chart 4. The number of studies combining MNPs and antifungal agents by drugs and fungal strains.

5.2.1 Method A

Method A was the most used strategy to obtain the dispersions with the conjugates. The MNPs were obtained by chemical, electrochemical or biological methods and the sizes varied from 1 and 68.7 nm in isolated MNPs or with 80 nm when stabilized onto zeolites (**Table 6**).

Table 6. Synergic studies between MNPs and antifungals obtained by the MNPs synthesis and their posterior combination with antifungals – method A.

MNPs, size (nm)	MNs synthesis	Reducing Agent	Stabilizing Agent	Combined antifungal agent	Fungi strains	Test method/Synergic results	Ref.
Ag, 1.0 - 50.0	Biogenic fungal	- Fungus <i>Aspergillus oryzae</i>	Biomass from <i>Aspergillus oryzae</i>	Fluconazole	<i>C. albicans</i> , <i>C. glabrata</i> , <i>C. parapsilosis</i> , <i>C. krusie</i> , <i>C. tropicalis</i> , <i>C. albicans</i>	MIC and FIC: <i>C. albicans</i> , <i>C. glabrata</i> , <i>C. parapsilosis</i> , <i>C. krusie</i> , <i>C. tropicalis</i> , <i>C. albicans</i>	162
Ag, 9.8	Biogenic bacteria	- Supernatant of Delftia sp. strain	Supernatant of Delftia sp.	Miconazole	<i>C. albicans</i> , <i>C. parapsilosis</i> , <i>C. aaseri</i> and <i>C. glabrata</i>	MIC: <i>C. albicans</i> , <i>C. parapsilosis</i> , <i>C. aaseri</i> and <i>C. glabrata</i> miconazole	163
Ag, 34.4- 68.7	Biogenic plant	- Phytochemicals from <i>Polyalthia longifolia</i>	n.a.	Amphotericin B	<i>C. albicans</i>	FIC: synergism	164
Ag, 24.1	Electrochemical	n.a.	PVP	Fluconazole and voriconazole	<i>C. albicans</i> clinical isolates	FIC: combinations	all 165
Ag-Zeolite, 80.0	Chemical	Trisodium citrate	Trisodium citrate	Fluconazole, caspofungin and micafungin	<i>C. albicans</i>	OD: <i>C. albicans</i> - caspofungin and micafungin	166

CuO, 6.5	Chemical	Sodium hydroxide	n.a.	Fluconazole	<i>C. albicans</i>	FIC: no synergism, just additive effect	167
ZnO, 35.0	Chemical	Sodium hydroxide	n.a.	Fluconazole	<i>C. albicans</i> isolates	ZoI and MIC: synergism	168
CuO, 50.0	n.a.	n.a.	n.a.	Fluconazole	<i>C. albicans</i>	FIC: no synergism, just additive effect	167
Ag, 8 - 12	Commercial	n.a.	PVP	Fluconazole	<i>C. albicans</i> SC5314 and clinical isolates	FIC: <i>C. albicans</i> clinical isolates	169
ZnO (pure and Mn, Cu, Co or Fe doped), 20.0	Commercial	n.a.	n.a.	Fluconazole and Amphotericin B	<i>A. fumigatus</i> , <i>C. albicans</i> , <i>C. neoformans</i> and <i>T. mentagrophytes</i>	FIC: <i>T. mentagrophytes</i> - amphotericin and ZnO doped	170

Kumar *et al.* (2014) tested the efficacy of AgNPs combined with miconazole against *Candida* strains, obtaining significant increased fungicidal activity. TEM and FTIR confirmed the NPs conjugation with miconazole. TEM images showed mono-dispersed nanoparticles with an average size of 9.8 and 23.9 nm for AgNPs and Miconazole-AgNPs, respectively. The FTIR spectra demonstrated similar functional groups of Miconazole in the conjugates, indicating the successful conjugation of the Miconazole drug to AgNPs.¹⁶³ Sun *et al.* (2016) studied the potential synergy between AgNPs and azole antifungals against drug-resistant *C. albicans*. Any inhibition of the drug-resistant *C. albicans* was observed using fluconazole or voriconazole alone. AgNPs alone had only the moderate killing ability. However, the combined treatment was effective against the drug-resistant *C. albicans*.¹⁶⁵ Li *et al.* (2018) referred to the combination of sub-lethal AgNPs and echinocandin drugs with potent synergistic effects against *C. albicans*.¹⁷¹ Weitz *et al.* (2015) tested the combination of CuONPs and fluconazole as a potential treatment against the pathogenic *C. albicans*. However, the results just showed additive effects.¹⁶⁷ Sharma *et al.* (2015) studied the antimicrobial activity of doped ZnONPs with manganese (Mn), copper (Cu), cobalt (Co) or iron

(Fe), where additive and synergistic effects were found depending on the dopant. ZnO doped with Mn (1 and 10%), Co (1 and 10%), or Cu (10%) showed antifungal synergistic results, and the other combinations just displayed additive effects.¹⁷⁰ MNPs-conjugates also presents a synergistic effect against biofilms. SEM images from miconazole-Fe₃O₄NPs against dual-species biofilms of *C. albicans* and *C. glabrata* revealed ruptures in the biofilms, generating less dense structures (Figure 2 e-f) than the untreated biofilm and also than the biofilms only treated with Fe₃O₄NPs, chitosan or miconazole (Figure 2).¹⁷²

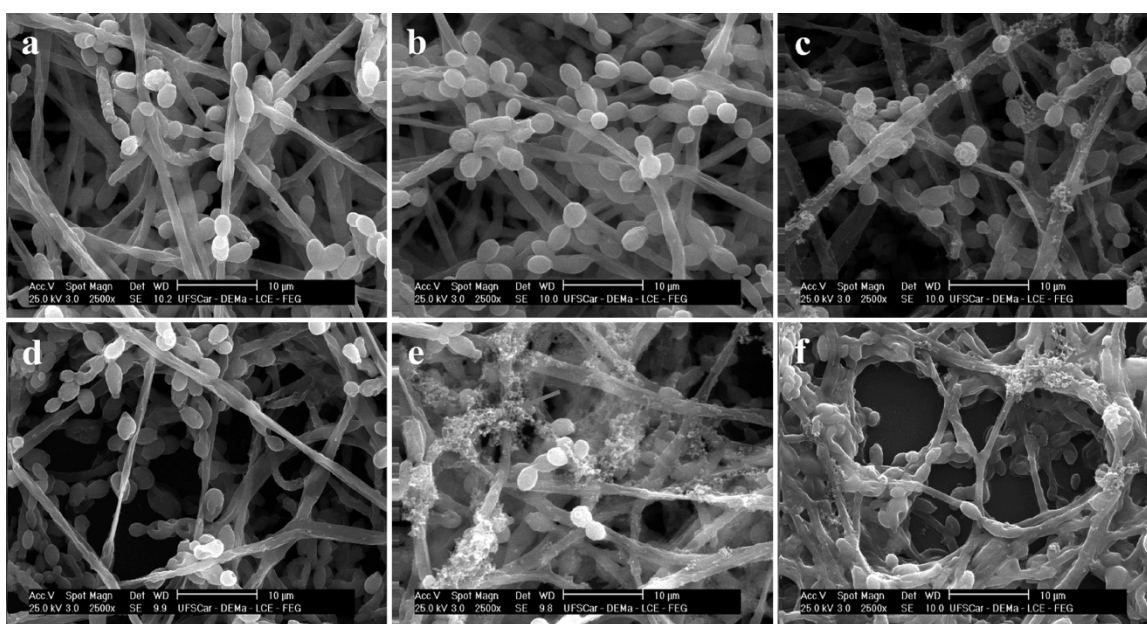


Figure 2. SEM images of dual-species biofilms of *C. albicans* and *C. glabrata* species (a) untreated and treated with (b) 110 µg.mL⁻¹ Fe₃O₄NPs (c) 110 µg.mL⁻¹ chitosan (d) 78 µg.mL⁻¹ miconazole and (e) miconazole- Fe₃O₄NPs conjugates at 31.2 (f) and 78 µg.mL⁻¹ at magnification of 2500x. Reproduced with permission from ref 172. Copyright 2020 Elsevier.

5.2.2 Method B

No works using method B for the conjugation of MNPs with antifungal agents were found in the literature.

5.2.3 Method C

Just 2 publications were found using method C. After MNPs synthesis, the MNPs were functionalized and combined with antifungals. In these works, the AgNPs were functionalized using N-[3-(trimethoxysilyl) propyl] diethylenetriamine (ATS) or 1-(3-(dimethylamino)propyl) 3-ethylcarbodiimidehydrochloride (EDC) and hydroxysuccinimide (NHS). Posteriorly, the functionalized NPs were mixed with ketoconazole and amphoteric B, respectively (Table 7).

Table 4. Synergic studies between MNPs and antifungals obtained by MNPs synthesis, subsequent MNPs functionalization and combination of antifungals – method C.

MNPs, size (nm)	MNPs synthesis	Reducing Agent	Stabilizing Agent	Combined antifungal agent	MNPs surface Functionalization method	Fungi strains	Antimicrobial results	Ref.
Ag, 15.0	Chemical	[N-[3-(trimethoxysilyl) propyl] diethylenetriamine] (ATS)	ATS	Ketoconazole	ATS under nitrogen atmosphere mixed with silver nitrate for 4h and mixed with antifungal.	<i>Malassezia furfur</i> clinical isolate	FIC: <i>M. furfur</i> - ketoconazole	173
Ag, 15.0	Biosynthesis	Extract of <i>Maytenus royleanus</i>	Plant extract and Amphotericin B	Amphotericin B	AgNPs in acetate buffer were mixed with EDC and NHS; then, the amphotericin B was added and kept under stirring for 4h.	<i>C. albicans</i> and <i>C. tropicalis</i>	ZoI: <i>C. albicans</i> and <i>C. tropicalis</i> - amphotericin B	174

AgNPs functionalized with ATS was mixed with ketoconazole, and the conjugates showed to be spherical in shape, and a stable dispersion was obtained (without any agglomeration). However, the interactions between AgNPs and ketoconazole was not studied. The synergistic effect was

observed in 17.08% of the isolates.¹⁷³ Amphoteric B-AgNPs also showed a spherical shape and were provided by an ester linkage promoted by the EDC molecules and hydroxyl groups from biomolecules in AgNPs surface. The conjugation of amphotericin B and AgNPs was assessed by UV-visible spectroscopy. The SPR peak of AgNPs alone (424 nm) red-shifted towards a longer wavelength by 24 nm (448 nm), indicating the conjugation of amphotericin B to AgNPs, which was well supported by FTIR and TEM results. AgNPs alone revealed low to moderate antifungal activity (ZoI 4-8 mm \pm 0.2). However, the amphotericin B conjugated AgNPs exhibited significant activity against *C. albicans* (ZoI 16 mm \pm 1.4) and *C. tropicalis* (ZoI 18 mm \pm 1.5).¹⁷⁴

5.2.4 Method D

Lastly, a particular case using method D - MNPs synthesis using antifungals as reducing agents was found (**Table 8**). Here, the amphotericin B acted as a reducing and stabilizing/capping agent in the AgNPs synthesis. The reaction occurred in an alkaline environment to prevent aggregation and promote AgNPs formation. This approach produced monodisperse AgNPs with 7 nm of size. Amphotericin B-AgNPs showed to be particularly effective against the most pathogenic fungi responsible for severe mycotic infections.¹⁷⁵

Table 8. Synergic studies between MNPs and antifungals obtained by MNPs synthesis using antifungals as reducing agents – method D.

MNPs, size (nm)	MNs synthesis	Reducing Agent/antifungal	Fungi strains	Antimicrobial results	Ref
Ag, 7.0	Chemical	Amphotericin B	<i>A. niger</i> , <i>C. albicans</i> and <i>F. culmorum</i>	ZoI: <i>A. niger</i> and <i>C. albicans</i> - amphotericin B	175

In summary, the combination of MNPs with antifungals can have additive and synergistic effects depending on the type of MNPs applied. A doping agent can further enhance the antifungal effect under certain conditions. Thus, considering the presented results, additional studies need to be performed to improve the knowledge and applicability in a broader range of pathogenic fungi.

5.3. Antivirals

Viral infections remain a major threat to global public health and have been responsible for alarming deaths. Viral infections can affect several tissues and organs, namely the upper respiratory tract and lungs (*e.g.* coronaviruses, rhinoviruses and influenza), the colon (*e.g.* rotavirus), the liver (*e.g.* hepatitis B virus (HBV)), the spinal cord (*e.g.* poliovirus), vascular endothelial cells (*e.g.* ebola), leukocyte (*e.g.* human immunodeficiency virus (HIV) and ebola), skin (*e.g.* herpes viruses and papillomaviruses) and neural cells (*e.g.* enteroviruses).¹⁷⁶⁻¹⁸⁰ During human history, several viruses outbreaks occurred, causing millions of deaths worldwide.¹⁸¹ Also, the current COVID-19 pandemic emerged at the end of 2019, and its health and economic impact continue to represent an exponential hurdle for the entire world.¹⁸² The strategies for antiviral drugs are focused on two different approaches: targeting the viruses themselves or the host cell. Antiviral drugs that directly target the viruses include the inhibitors of virus attachment, virus entry inhibitors, uncoating inhibitors, polymerase inhibitors, protease inhibitors, inhibitors of nucleoside and nucleotide reverse transcriptase and the inhibitors of integrase. The inhibitors of protease (ritonavir, atazanavir and darunavir), viral DNA polymerase (acyclovir, tenofovir, valganciclovir and valacyclovir) and integrase (raltegravir) are listed among the Top 200 Drugs by sales during the 2010s.¹⁸³ Another antiviral agent class is the neuraminidase inhibitors (oseltamivir, zanamivir and peramivir), broadly used against influenza. The adamantanes (amantadine) act by blocking the

ion channel of the influenza virus, but it is rarely used due to the high resistance of the circulating strains.^{184, 185} Thus, the approved drugs that present an inhibitory spectrum against nine human infectious diseases can be recapitulated as follows: human immunodeficiency virus (HIV), human cytomegalovirus (HCMV), HBV, hepatitis C virus (HCV), herpes simplex virus (HSV), influenza virus, respiratory syncytial virus (RSV), varicella zoster virus (VZV) and human papillomavirus (HPV). The drugs may be administrated as mono or combined therapies.¹⁸⁶

Despite the advances reached during the last years, new strategies are needed to tackle several critical unsolved issues in antivirals: resistance mechanisms, poor permeability through cell membranes, low selectivity, low stability during storage and application, and unable to withstand the conditions of the gastrointestinal tract (hindering the oral administration). Moreover, antivirals are renowned for their high cost and toxicity. One of the most common and critical toxicity is related to their proneness to crystallize, which may cause acute kidney failure, seriously limiting therapy concentration.^{187 187-189}

Some of these limitations can be overcome using nanotechnology once it is possible to design the nanoparticles (*e.g.* composition, morphology, dimensions and surface characteristics) to improve the handling, stability, absorption and potency of antivirals.¹⁹⁰ Most of the research studies comprising nanoparticles and antiviral agents aim to use nanoparticles as delivery systems, and very few analyze the synergistic antiviral effects that may occur. Different nanomaterials have been studied as delivery vehicles for antiviral drugs, including lipids, polymers, lipids–polymers hybrids, carbon and metals.¹⁹¹ Inorganic nanoparticles present some advantages when compared to organic ones. They are easier to functionalize and possess fewer storage requirements since they are not sensitive to microbial or hydrolytic degradation.¹⁹² MNPs have been widely explored for their antiviral activity per se, namely: Ag, Au, CuO, SiO₂, TiO₂ and CeO₂. These nanoparticles

have exhibited pronounced efficacy against several viruses such as influenza (H3N2 and H1N1), HBV, HSV, HIV-1, dengue virus type-2, foot and mouth disease virus and vesicular stomatitis virus. The MNPs functionalization with silane or thiol groups have been displayed to improve the interaction of MNPs with biomolecules. They simultaneously enhanced the impedance of viral internalization in cells and allowed the release of the antiviral drugs.¹⁹¹ The research works combining MNPs and antiviral agents are very limited, and only 4 studies against influenza H1N1 virus were found in the literature using AgNPs (3 studies) and AuNPs (1 study) (**Table 9**).

Table 5. Studies between MNPs and antiviral agents obtained by the MNPs synthesis in the presence of antivirals – method B.

MNPs, (nm)	size	MNs synthesis	Reducing Agent	Stabilizing Agent	Combined antiviral agent	Virus	Antimicrobial results	Ref.
Ag, 2.0		Chemical	Vitamin C	n.a.	Zanamivir	H1N1	Synergism	¹⁹³
Ag, 2.0		Chemical	Vitamin C	n.a.	Amantadine	H1N1	Synergism	¹⁹⁴
Ag, 2.0		Chemical	Vitamin C	n.a.	Oseltamivir	H1N1	Synergism	¹⁹⁵
Au, 2.0		Chemical	Sodium borohydride	Oseltamivir	Oseltamivir	H1N1	n.a.	¹⁹⁶

Here, just chemical methods were found to prepare the MNPs, and all the studies used method B to prepare the MNPs-conjugates dispersions. These conjugates displayed interesting synergistic effects. The MNPs were combined with antiviral drugs approved to treat H1N1 infections (zanamivir, amantadine and oseltamivir). The AgNPs-antiviral conjugates depicted monodisperse, highly uniform 2 nm spherical particles. Curiously, the AgNPs before functionalization possessed 3 nm. The superior stability was due to an increase in the zeta potential.¹⁹³⁻¹⁹⁵ Li *et al.* (2016-2017) prepared zanamivir, amantadine and oseltamivir modified AgNPs and investigated the suppression

mechanisms of H1N1 viral infections. The conjugates exhibited notable thermodynamics and kinetics stability. More importantly, they displayed evident synergistic virus inactivation properties against the influenza virus.^{193-195, 197} Stanley *et al.* (2012) studied, for the first time, influenza therapeutics and diagnostics targeting the neuraminidase (instead of the hemagglutinin) combining AuNPs and oseltamivir. It was observed that the conjugates interacted with the virus neuraminidase rather than the hemagglutinin. This highlighted the potential of the conjugates to work as novel influenza virus sensors.¹⁹⁶ Although the promising results, applying these concepts in a clinical environment still requires enormous researcher effort.

6. Mechanism of action and resistance

The conjugation of MNPs and commercial antimicrobial drugs provides conditions to improve antimicrobial activity. The conjugation of MNPs and antimicrobial drugs allow the simultaneous activation of several *modus operandi*. However, their mechanism of action is still poorly understood. This section analyses the studies performed to understand the mechanism of action and resistance of the MNPs alone or in combination with antibiotics, antifungals and antivirals. The MNPs and common antimicrobial agents display different mechanisms of action and, consequently, distinct resistance strategies.

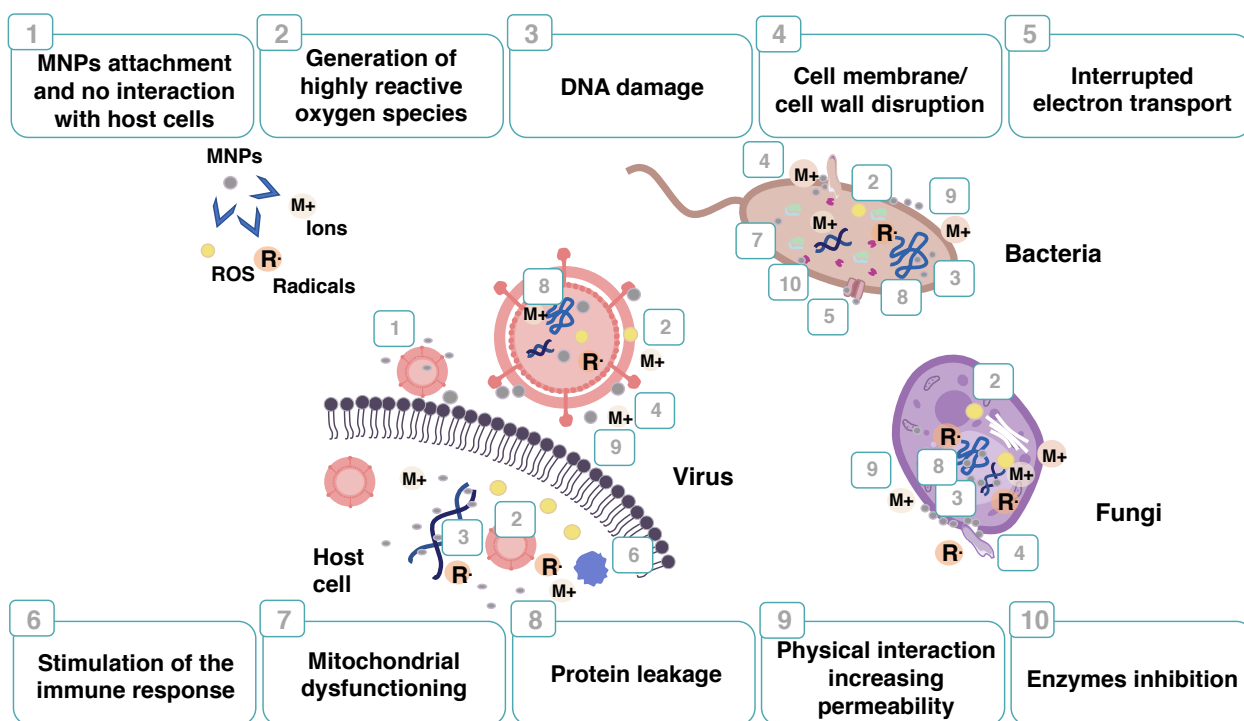
6.1. MNPs

The antimicrobial mechanism of MNPs is not entirely understood, but it is possible to follow the sequence of events that influence their action as reported in **Scheme 3**. First, the electrostatic interactions of MNPs with the phospholipid layer of the cell membrane or cell wall components may induce their disruption. Adsorption of MNPs leads to cell wall depolarization, changing the

typically negative charge of the wall that becomes more permeable. Due to the disruption, water from the cytosol is released, and the cells try to compensate for the loss through proton efflux pumps and electron transport. Therefore, the microorganism homeostasis is severely compromised due to the imbalance of ions which impair respiration, interruption of energy transduction and, ultimately, cell death. Moreover, the interactions of MNPs with sulphur-containing molecules within the cell membrane and the metal ions hinder cell wall synthesis. Another antibiotic mechanism of action is the production of ROS and the release of metal ions. These species can denature proteins, damage RNA, DNA, and lipids. Thus, if the cell antioxidant defenses are overwhelmed, ROS can influence the cell wall and membrane permeability, impair enzymatic activity, protein translation, inhibit ATP production and genetic material replication. The capping agents of MNPs have an important influence in these steps once they can improve or reduce the release of ROS or ions. The MNPs and ions can also bind to cytosolic proteins such as enzymes and nucleic acids.^{198, 199}

The antiviral function of MNPs can be due to the inhibition of the virus penetration into the cell by the MNPs linkage with the virus and stimulation of the nucleus to increase the immune response of the host cell.²⁰⁰

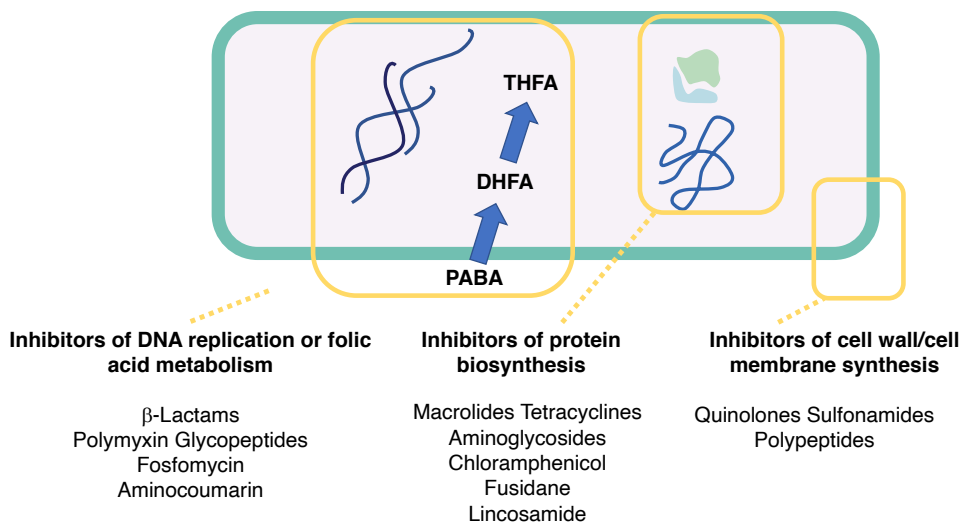
Some of the newly reported MNPs resistance mechanisms comprise electrostatic repulsion, ion efflux pumps under non-bactericidal concentrations, expression of extracellular matrices and the adaptation through mutations.²⁰¹ However, more studies are needed to unravel the mechanisms behind each of these processes.



Scheme 3. Mechanism of action of MNPs as antimicrobial agents.

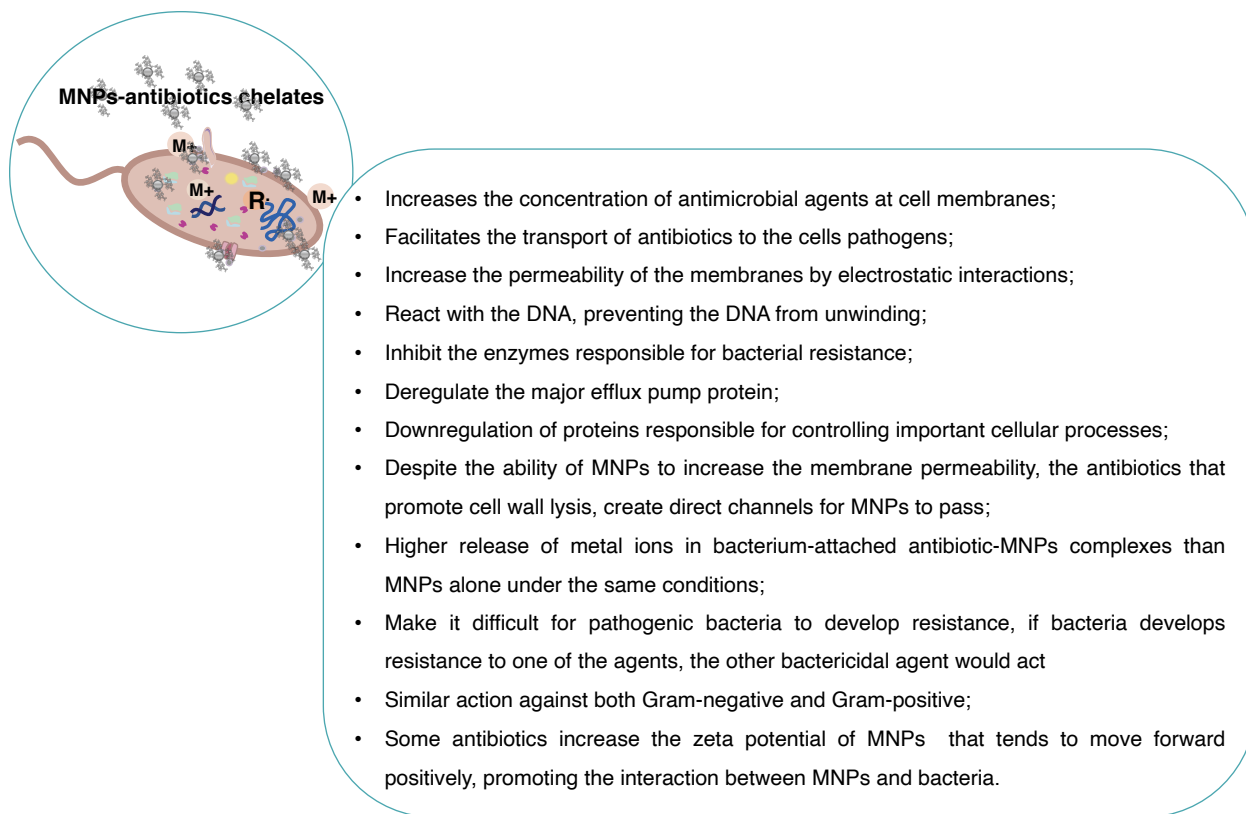
6.2. Antibiotics

Antibiotics *modus operandi* are well known and may be divided by their specific targets: biosynthesis (cell wall and proteins), genome replication, and folic acid metabolism (**Scheme 4**).²⁰² However, several resistance mechanisms emerged with the appearance of enzymes able to destroy the antibiotic structures, namely β -lactamase enzyme and chloramphenicol acetyltransferase. Furthermore, mutations in the antibiotics targets, for example, in the enzyme dihydropteroate synthase (DHPS) (the target of sulphonamides), and overexpression of efflux pumps, reduced the drug accumulation.²⁰³⁻²⁰⁸ Resistance may also occur by replacing the negatively charged groups in the bacterial membrane by neutral groups, thus diminishing the potential electrostatic interaction with MNPs and antibiotics. In addition, genetic mutations may unfold in encoded transport systems.²⁰⁹⁻²¹³



Scheme 4. Mechanism of action of antibiotics.

The synergistic mechanism of action of combined MNPs and antibiotics is described in **Scheme 5**. Several works studied the bonding between antibiotics and MNPs by chelation. This chelation increases the concentration of antimicrobial agents at specific points on the cell membrane, where MNPs, acting as a drug carrier, facilitate the transport of antibiotics to the cell surface. In particular, the affinity of AgNPs and AuNPs to sulphur-containing proteins of the bacterial cell membrane enhances the interactions with cells, increasing the permeability of the membranes. This facilitates the infiltration of the antibiotics into the cell. The MNPs-chelates can also react with the DNA increasing the unwound DNA, which due to its higher susceptibility to damage, may result in lethal mutations.^{89, 117, 119, 153}



Scheme 5. Advantages of MNPs-antibiotic conjugates and their mechanism of action.

The enzymes responsible for the antibiotic hydrolysis, such as lactamase and carbapenemase, may be inhibited by MNPs, maximizing antibiotic activity.¹⁰¹ Gupta *et al.* (2017) used ethidium bromide (EtBr), which is widely used as a substrate for efflux pumps in cells, to determine the ability of MNPs to act as efflux pump inhibitors. *E. coli* was incubated with hydrophobic AuNPs, and downregulation of the expression of the efflux pumps was observed. The efflux pumps are renowned for their contribution to antibiotic resistance for their role in detoxification. Furthermore, some of the proteins responsible for the assembly of the bacterial outer membrane proteins were strongly deregulated, compromising the integrity of the cell wall. Therefore, synergism between MNPs and antibiotics may be potentiated by the deregulation of major efflux pump proteins.

The hydrophobic nanoparticles can also interact with multiple proteins to disrupt crucial cell survival processes, enhancing the efficacy of the antibiotic.¹⁴⁹ Wei *et al.* (2007) conjugated AgNPs with norvancomycin. They observed that the permeability of the outer membrane was affected by the AgNPs attachment to the lipopolysaccharide membranes, leading to its destabilization and allowing the norvancomycin action.¹⁴⁸ Fayaz *et al.* (2010) explained the ampicillin-AgNPs mechanism against bacteria. First, the ampicillin molecules surround AgNPs by electrostatic attraction. Then, the ampicillin promotes the cell wall lysis creating channels that allow the penetration of AgNPs into the bacteria. The ampicillin-AgNPs complex reacts with DNA and prevents DNA unwinding, which seriously compromises cell viability.¹¹⁸ Bhande *et al.* (2013) provided a possible explanation for enhancing synergistic antibacterial mechanism of β -lactam antibiotics and ZnONPs. The contact of ZnONPs with the cell wall and consequent penetration is more accessible when surrounded by β -lactam antibiotics. Inside the cell, the ZnONPs–antibiotic complex reacts with DNA resulting in critical genome damage.¹⁰⁷ Another research work showed a higher release of metal ions in antibiotic-MNPs complexes than AgNPs alone under the same conditions. They were being observed a localized transient high metal ions concentration near the bacterium's surface. The metal ions bind to proteins and nucleic acids, causing bacterial death.¹⁰³

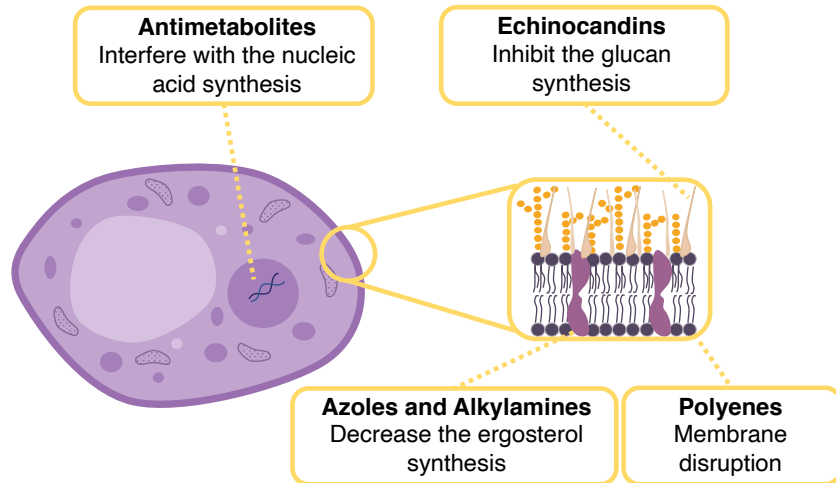
These studies suggested that simultaneous action of antibiotics and AgNPs will make it difficult for pathogenic bacteria to develop resistance. If bacteria develops resistance to one agent, the other bactericidal mechanism will kill the bacteria.^{94, 123} Another interesting and important fact was the similar synergistic effects against both Gram-negative and Gram-positive bacteria, indicating that the difference in cell wall composition did not influence synergistic efficiency.¹⁰¹ In addition, the size and surface properties of MNPs can directly influence the synergistic effects of MNPs when

combined with antibiotics. In synergistic studies, smaller MNPs showed to improve the antimicrobial properties. The effect of the capping agent was also described, and the results showed a more prominent effect with PVP-capped AgNPs as compared to citrate- and SDS-capped ones. As expected, the more positive is the charge of MNPs, the better the antibacterial action is. When the antibiotic gentamicin was added to a MNPs dispersion, the zeta potential of MNPs displayed a more positive charge, promoting the interaction between MNPs and bacteria.⁹⁸ Experimental data related to synergistic effects of different shaped AgNPs with various antibiotics have not been reported yet in the scientific literature.¹⁰¹ A long-lasting, single-particle treatment capable of overcoming antibiotic resistance would be highly beneficial in the clinical environment.²¹⁴

6.3. Antifungals

Antifungal drugs mainly have two targets: cell membrane or nucleic acid synthesis. The azoles, alkylamines, polyenes, and echinocandins destabilize the cell membrane, and antimetabolites interfere with nucleic acid synthesis (**Scheme 6**).

Most of the resistance mechanisms related to antifungal drugs involve target modifications or overexpression of efflux pumps that expel the drug out of the cell, decreasing its intracellular concentration. The target mutation and/or target expression deregulation is another resistance mechanism. For example, the ERG11 gene encodes the enzyme lanosterol 14 α -demethylase in yeasts, the target enzyme for azoles. Thus, mutations or overexpression in this gene alters the azole-binding site, requiring a higher drug concentration. The last mechanism in antifungals' resistance is attributed to alterations in the ergosterol biosynthesis pathway, where the mutation in the gene encoding the lanosterol 14 α -demethylase enzyme also modifies other enzymes from the same biosynthetic pathway.^{215, 216}

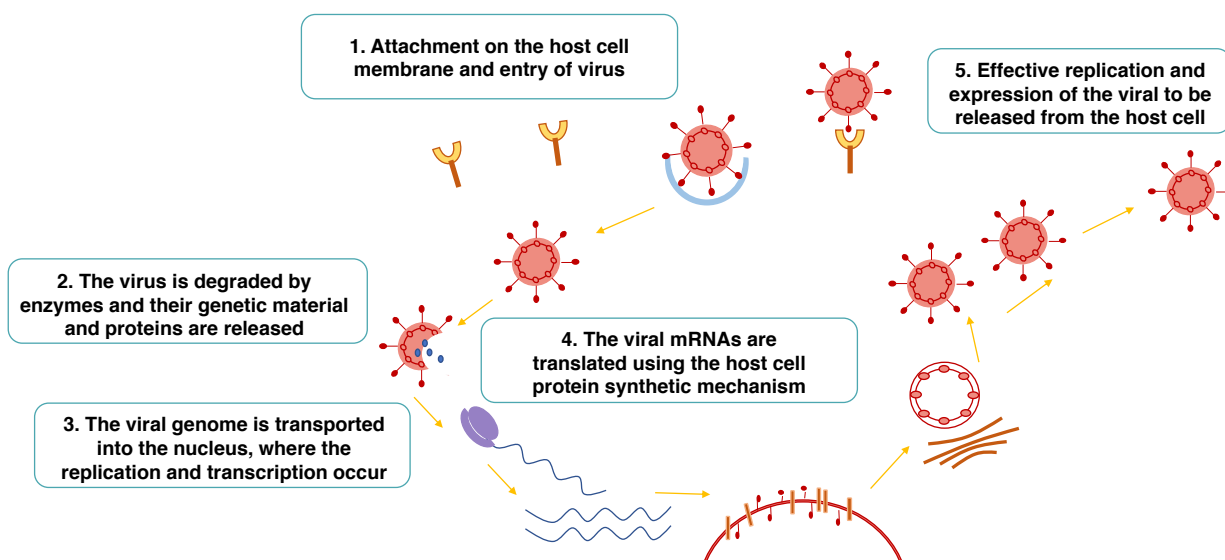


Scheme 6. Mechanism of action of antifungal agents.

Few studies about the mechanism of action of MNPs combined with antifungals can be found in the literature. Kumar *et al.* (2014) mentioned that the conjugation of AgNPs with miconazole increased the drug's efficacy and played a dual mechanism of action by ROS accumulation and inhibition of the ergosterol biosynthesis.¹⁶³ Sun *et al.* (2016) showed that the binding of PVP-coated AgNPs with fluconazole enhanced the antifungal properties. The author theorizes that the antifungal action may be due to the re-modelling of the cell membrane in the azole-resistant strains or to an azole transport-specific mechanism. The researchers also noted an increased inhibition of the normal budding process. The mechanism of synergy between PVP-AgNPs and nystatin or chlorhexidine digluconate was attributed to the actions of both MNPs and antifungal drugs. On the opposite, the synergy mechanism between PVP-AgNPs and fluconazole or voriconazole was attributed to the MNPs tendency to adhere to the cell membrane and inhibit the budding replication. In addition, the dysregulations of the ergosterol pathway and efflux pumps may serve as a crucial contributor to the synergy between PVP-coated Ag and fluconazole or voriconazole.¹⁶⁵

6.4. Antivirals

The development of antiviral agents is challenging, even though the existing similarities in infection processes. Viral infection progression may be considerably different among distinctive strains. The most frequent stages in viral infections are: i) attachment, ii) penetration, iii) uncoating, iv) gene expression and replication, v) assembly, and vi) release (**Scheme 7**). Antiviral drugs are designed to block one or more of these steps.^{188,217}



Scheme 7. Mechanism of viral infection.

The available antivirals are frequently restricted by their short spectrum, the rapid emergence of drug resistance and toxicity.²¹⁸ The approved antiviral drugs include: 5-substituted 2'-deoxyuridine analogues, nucleoside analogues, (nonnucleoside) pyrophosphate analogues, nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, entry inhibitors, acyclic guanosine analogues, acyclic nucleoside phosphonate analogues, hepatitis C virus NS5A and NS5B inhibitors, influenza virus inhibitors and immunostimulators, interferons, oligonucleotides, and antimetabolic inhibitors.¹⁸⁶

A major challenge facing antiviral drug development is resistance. Indeed, drug resistance is a commonly reported issue affecting approved antiviral drugs that directly act against a viral target or virus-host interaction. Drug resistance is particularly problematic concerning RNA viruses, due to their rapid rate of viral replication and frequent recombination events. The availability of novel drugs with different mechanisms of action or combination therapy can improve the treatment outcome.²¹⁹ It was previously assumed that viruses could not develop drug resistance against agents that target host factors needed for virus replication once viruses cannot easily replace the missing cellular functions by mutagenesis. However, emerging evidence suggests that viral resistance against host-directed antiviral agents can occur by mutations, such as in fusion protein, mutations near the active site, RNA-dependent RNA polymerase, viral proteins, viral polymerase and envelope proteins. While not yet fully understood, one possible mechanism underlying the acquisition of drug resistance against host-directed agents is that the virus may use an alternate host factor. Other examples include viruses that have evolved diverse strategies to modulate host translational apparatus. The most understood mechanism of antiviral drug resistance against virus-directed therapies is that mutations occur in the viral genome at druggable sites. These alter viral susceptibility to the direct action of drugs. Moreover, the precise nature of host factors that may regulate the phenomenon of drug tolerance remains elusive. Model systems are urgently required to evaluate drug resistance/synchronization under complex and dynamic settings, such as drug combinations, multiple viral infections, and seasonality.²²⁰

The antiviral mechanism of action of conjugates is an unexplored field. Just one group of researchers studied the mechanism of action of an antiviral drug against the influenza virus. Li *et al.* (2016) revealed that AgNPs-amantadine/oseltamivir could block the H1N1 virus from infecting host cells and preventing DNA fragmentation, chromatin condensation and activity of caspase-3.

The conjugates inhibited the accumulation of reactive oxygen species (ROS) and reversed virus-induced apoptosis by the H1N1 virus.^{194,195} The same group in 2017, used flow cytometric analysis and TUNEL–DAPI assay to evaluate the antiviral mechanisms of AgNPs-zanamivir. The potential molecular mechanisms revealed that AgNPs-zanamivir inhibited caspase-3 mediated apoptosis via ROS generation.¹⁹³ Overall, the synergistic action and the mechanism behind them showed several advantages, but most studies are highly speculative and need further investigation. However, the topic requires more exploration. It is crucial to investigate the effects of MNPs with other drugs to fully understand the bioeffects of these complex systems in the virus.

7. Cytotoxicity

Cytotoxicity of human exposure to MNPs has rightfully gained attention in the last years. Since these nanomaterials have been intentionally engineered to interact with cells in biomedical applications, it is important to ensure that these activities do not create adverse effects on the human body.²²¹ The negative effects of MNPs are related to their physical and chemical properties, including the size, shape, surface charge, chemical compositions (core and shell) and stability. Many types of MNPs are not recognized by the cells protective systems of the human body, which decreases the rate of their degradation and may lead to considerable accumulation of nanoparticles in organs and tissues, resulting in highly toxic and lethal concentrations. Several approaches to design new nanoparticles with lower toxicity than traditional nanoparticles are already available. Advanced methods for studying the toxicity of the nanoparticles make it possible to analyze different pathways and mechanisms of toxicity at the molecular level, and predict possible negative effects on the body. The data relating to the adverse and toxic effects of AgNPs differs strongly in literature, and several conclusions are controversial.²²² Moreover, commercial antimicrobial drugs

(antibiotics, antiviral and antifungal) show several issues related to their tolerance. Antibiotic resistance and toxicity are the major limiting factors in the use of antibiotics. Antibiotics toxicity can cause hypersensitivity reactions, blood dyscrasias, nephrotoxicity, neurotoxicity, ototoxicity, hepatic and renal toxicity.²²³ In antifungal therapies, hepatotoxicity incidence rates are induced by antifungal therapy with azoles.²²⁴ Despite polyenes' highly favorable antifungal activity, the treatment remains difficult due to toxicity in critical mammalian organ systems, mainly nephrotoxicity, caused by its lack of selectivity between fungal and animal sterols. The antimetabolites have expressed hepatotoxicity and bone marrow depression in combination therapies.^{225, 226} The antiviral drugs have been related to nephrotoxicity (even in low doses) (adefovir), renal and bone toxicity (patients with HIV) and high level of renal toxicity (acyclovir).^{186, 227} In synergistic studies involving MNPs and commercial antimicrobial drugs, testing the cytotoxicity is a factor of extreme importance. However, only the more recent reports (since 2015) include cytotoxicity tests for conjugates. A careful analysis of the literature found only 17 works discussing the toxicity of the conjugates. These studies were carried out using colorimetric tests namely 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay or 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. The tests were performed with mortal cells such as NIH 3T3 fibroblasts, keratinocytes HaCaT, human embryonic kidney cells (HEK293T), human colon epithelial cells (CCD-841CoTr), human retinal pigment epithelial-1 (RPE-1), human gingival fibroblasts (MD-HGF) and mouse peritoneal macrophages. In addition to immortal cells: human acute monocytic leukemia cells (THP-1), human breast cancer cell (MCF7) and rat glioma cells C6 (**Table 10**).

Table 10. Cytotoxicity synergic studies between MNPs and combined commercial antimicrobial agent.

MNPs, size (nm), stabilizing agent	Combined commercial antimicrobial agent	Pathogens	Cell lines	Test: cytotoxicity result	Ref.
Ag, 7.4 - 18.3, n.a.	Cefotaxime	<i>E. coli</i> and MRSA	MCF-7 and RPE-1 cells	MTT: no cytotoxic effect on normal cells at even 12 µg/mL for 24 hrs.	126
Ag, PVP 12.0,	Ampicillin	DH5α susceptible and ampicillin-resistant <i>E. coli</i> strains	HEK293T	MTS assay: no significant viability reduction	147
Ag, citrate 23.0,	Tetracycline, neomycin and penicillin G	<i>S. typhimurium</i> DT104 (ATCC 700408)	HaCaT	MTS assay: tetracycline-AgNPs was not toxic; penicillin-AgNPs was slightly toxic to cells; neomycin-AgNPs slightly stimulated HaCaT cell growth at the 24 h exposure time	97
Ag, n.a. 25.0,	Vancomycin	<i>S. aureus</i> and <i>E. coli</i>	Mouse peritoneal macrophages	MTT: no cytotoxic effect at the 0.05 mM, 0.1mM and 0.3mM concentration after 24 h.	99
Ag, n.a. 26.0,	Erythromycin, ampicillin, chloramphenicol, clindamycin, tetracycline, gentamycin, amoxicillin, ciprofloxacin, ampicillin, cefpodoxime and cefuroxime	<i>S. aureus</i> , MRSA, <i>S. mutans</i> , <i>S. oralis</i> , <i>S. gordonii</i> , <i>E. faecalis</i> , <i>E. coli</i> , <i>actinomycetemcomitans</i> and <i>P. aeruginosa</i>	MD-HGF	Live/dead assay: using a low concentration of AgNPs (1.0 mg/mL), the viability of primary human fibroblasts was over 80% even after 7 days of direct culture with the AgNPs.	100
Ag, gelatin 26,	Ampicillin, Ampicillin/Sulbactam, Cefazolin, Cefuroxime, Cefoxitin, Gentamicin, Co-trimoxazole, Colistin, Oxolinic acid, Ofloxacin, Tetracycline, Aztreonam, Piperacillin, Piperacillin/Tazobactam, Meropenem, Ceftazidime, Cefoperazone, Cefepime, Amikacin, Ciprofloxacin, Penicillin, Oxacillin, Chloramphenicol,	<i>E. coli</i> CCM 4225, <i>P. aeruginosa</i> CCM 3955 and <i>S. aureus</i> CCM 4223	NIH/3T3	MTT assay: >70% of cells viability in tests with MIC concentration, >90% using sub-MIC concentration	101

		Erythromycin, Clindamycin, Ciprofloxacin, Teicoplanin Vancomycin	and			
Ag, 28, n.a.		Cefotaxime, ceftazidime, meropenem, ciprofloxacin gentamicin	and	Susceptible and resistant <i>E. coli</i> and <i>K. pneumoniae</i>	NIH/3T3	MTT assay: AgNPs, antibiotics alone and AgNPs-antibiotics combinations at concentrations of 4 mg/L and 2 mg/L, respectively, showed no cytotoxic effect on the mammalian cell lines ¹⁰²
Ag, n.a.	44.1,	Ampicillin		<i>E. coli</i> , <i>S. aureus</i> , ampicillin resistant <i>E.</i> <i>coli</i> , <i>S. aureus</i> , multi drug resistant <i>P. aeruginosa</i> and <i>K. pneumonia</i>	HaCaT	MTT assay: non-toxic ¹⁵²
CuS, n.a.	15.0,	Vancomycin		<i>E. faecium</i> and <i>E. faecalis</i>	3T3 and C6	MTT assay: slightly reduced cell viability was yielded when cells were treated with conjugates at the concentration of 16 µg/mL upon NIR irradiation ¹⁵⁴
Ag-Zeolite, 80.0, citrate		Fluconazole, casprofungin micafungin	and	<i>C. albicans</i> 451	HUVEC	MTT assay: cytotoxicity similar to AgNPs alone ¹⁶⁶
Ag, B	7.0, amphotericin	Amphotericin B		<i>A. niger</i> , <i>C. albicans</i> and <i>F. culmorum</i>	CCD- 841CoTr and THP-1	MTT assay: >80% of cells viability to Amphoteric B- AgNPs (1:11 molar ration) ¹⁷⁵
Ag, 2.0, n.a.		Amantadine		H1N1	MDCK	MTT assay: >90% of cells viability ¹⁹⁴
Ag, 2.0, n.a.		Oseltamivir		H1N1	MDCK	MTT assay: >90% of cells viability ¹⁹⁵

Khatoon *et al.* (2019) tested the cytotoxicity of ampicillin-AgNPs against keratinocytes cell lines HaCaT. The conjugates were found non-toxic to mammalian cells with significant antibacterial activity against ampicillin-resistant and multidrug-resistant bacteria.¹⁵² McShan *et al.* (2015) evaluated the cytotoxicity of the tetracycline, neomycin, penicillin G and AgNPs on HaCaT cells to understand whether AgNPs and antibiotics alone or their combination are toxic to human cells

in three exposure periods (0.5, 2, and 24 h). They also tested the silver nitrate cytotoxicity as a control. AgNO₂ was toxic, and its toxicity increased throughout the experiment. At the same concentration, AgNPs showed no toxicity. Also, the three antibiotics were non-toxic up to 16 μM. The conjugates tetracycline-AgNPs were not toxic for all three exposure times- Penicillin-AgNPs was slightly toxic to cells, while neomycin-AgNPs slightly stimulated HaCaT cell growth after 24 h of exposure.⁹⁷ Panáček *et al.* (2016) assessed the cytotoxicity of AgNPs, antibiotics with a different mode of action and their combinations at concentrations equal to and under the MIC values. In the case of cytotoxicity evaluation at concentrations similar to MIC values, AgNPs and antibiotics only slightly inhibited the viability of cells. When antibiotics were combined with AgNPs, the viability of cells decreased from 85% to 71% compared to the control. The cytotoxic effect was higher due to the additive cytotoxic of the antibiotics and AgNPs. A combination of antibiotics and AgNPs shows the highest inhibition of cell's viability at concentrations equal to their MIC. In the studies at lower concentrations, below MIC, but still showing antibacterial activity, the agents did not hinder cell viability. When antibiotics were combined with AgNPs, the viability of cells only decreased to 90%–95% compared to the control. It may be assumed that prevention or treatment of infections would be more effective when antibiotics combined with AgNPs occurred at very low concentrations of both antimicrobial substances, minimizing the risk of toxic side effects. Since no cytotoxic was observed in NIH/3T3 cells. However, the adequate dose to be used is still unclear, thus requiring further research to determine if AgNPs combined with antibiotics can be effective for the local and systematic therapy of infectious diseases without showing any side or adverse effects.¹⁰¹ Oliveira *et al.* (2017) studied the possible cytotoxic effect of the Ag-SiO₂ or Ag-SiO₂-Ampicillin at the highest concentration used during bactericidal tests, using HEK293T cells. Ag-SiO₂ system showed a strong cytotoxic effect for both treatment periods,

reducing the cell viability to approximately 20% after 48h of incubation. On the other hand, Ag-SiO₂-Ampicillin showed promising results since no significant viability reduction was observed. The researchers also studied the mitosis phases of Ag-SiO₂-Ampicillin-treated HEK293T cells. The observation during the three mitosis phases: prophase, metaphase and anaphase, suggest that, for at least 48 h, almost no toxicity or cell growth inhibition was observed in the presence of Ag-SiO₂-Ampicillin and that the antibiotic probably acts as a toxic-protective organic molecule. MNPs coated with ampicillin were not able to interfere during the cellular metabolism since different mitosis cell phases were seen in the presence of Ag-SiO₂-Ampicillin (**Figure 3**).¹⁴⁷

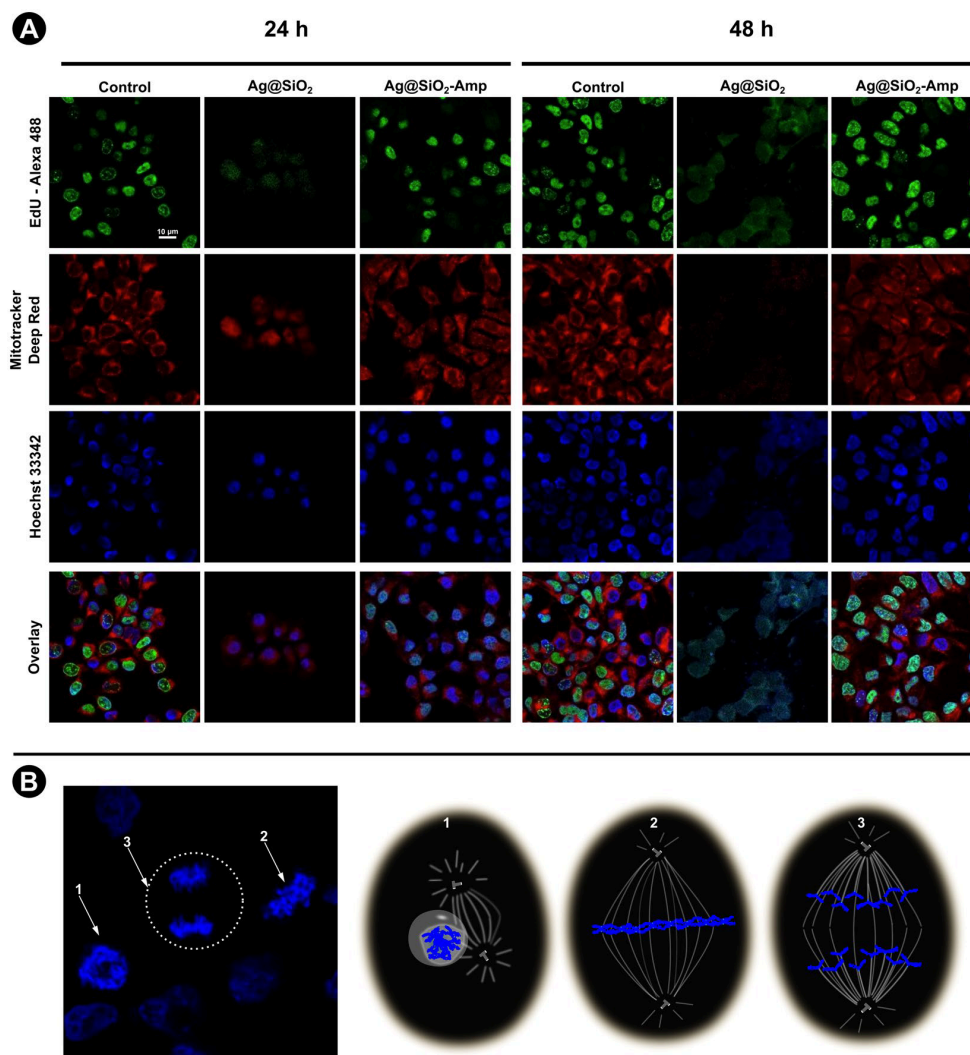


Figure 3. Cells images during the cytotoxicity tests: (A) First column corresponds to the control test in the absence of nanoparticles for 24 and 48 h of treatment (just ampicillin), the second column corresponds to the cells in the presence of the Ag-SiO₂, and the third column corresponds to the cells in the presence of the Ag-SiO₂-Ampicillin. “EdU-Alexa 488” line represents proliferating cells; “MitoTracker® Deep Red” line indicates mitochondria in the cytoplasm; “Hoechst 33342” line represents the cell nuclei, and the last line represents the overlay of the three images for each condition. (B) Mitoses phases were observed in confocal images. White arrows in confocal image and schemes 1, 2 and 3 represent prophase, metaphase and anaphase, respectively, after 48 h of Ag-SiO₂-Ampicillin treatment. Reproduced with permission from ref 147. Copyright 2017 Springer Nature.

Li *et al.* (2018) evaluated the drug combination of AgNPs at sublethal concentrations with echinocandin drug. The authors tested the toxicity of the combination with HUVECs mammalian cells. Combining an echinocandin drug and a sub-lethal dose of 80 nm AgNPs showed relatively low cytotoxicity to mammalian cells. Thus, the combination of echinocandin drugs and AgNPs at sub-lethal levels could become a new strategy for the clinical treatment of infections with antifungal resistant strains or even for new drug development.¹⁶⁶ Tutaj *et al.* (2016) tested the cytotoxicity of amphotericin B-AgNPs in CCD-841CoTr and THP-1 cell lines since colon epithelial cells serve as a model to evaluate amphotericin B transport across the intestinal barrier and monocytes can accumulate the drug. The results of cytotoxic studies revealed the statistically lower toxicity of Amphoteric B-AgNPs (1:11 molar ration) in comparison with amphotericin B alone (>80%). The differences might be due to the different molecular organization of amphotericin B in each formulation. The amphotericin B alone is in the aggregated form, while in

the nano-formulations, amphotericin B is in the monomeric state due to immobilization of the molecule on the MNPs surface.¹⁷⁵ Li *et al.* (2016) studied the cytotoxic effects of the H1N1 influenza virus on MDCK cells and the protective effects of Amantadine-AgNPs and oseltamivir-AgNPs by MTT assay. MDCK cells treated with the H1N1 influenza virus showed cell viability of 39%. Amantadine, oseltamivir and AgNPs increased the cell viability to 56%, 59% and 65%, respectively. However, the cell viability was increased to 90% by Amantadine-AgNPs or Oseltamivir-AgNPs combinations.^{194, 195} A change of the morphology of MDCK cells treated with the Oseltamivir-AgNPs was observed by TEM. The microvilli and mitochondria showed no morphological alterations in the untreated cells. When incubated with the H1N1 influenza virus, TEM image indicated cells with the disappearance of microvilli, a shrinking cytoplasm, distorted organelles and condensed chromatin, indicating apoptosis of the MDCK cells. The percentage of cells that lost adhesion and shrunk was decreased after treatment with Oseltamivir-AgNPs (**Figure 4**).¹⁹⁵

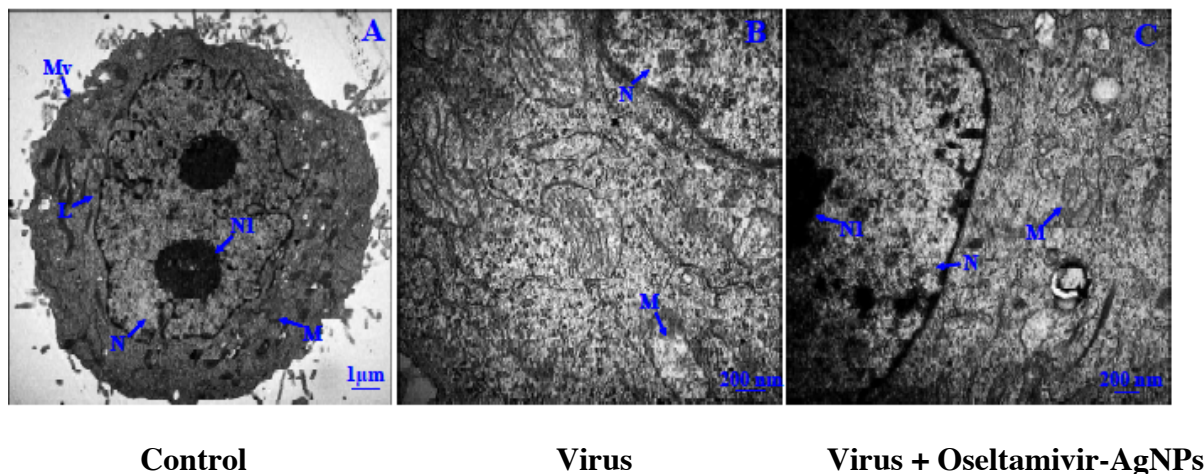


Figure 4. TEM images of thin sections of MDCK cells treated with (A) Control, (B) Cell treated with virus and (C) Cell treated with virus and Oseltamivir-AgNPs (N: nucleus; N1: nucleolus; M: mitochondria).

mitochondria; L: lysosome; Mv: microvillus; Ag: silver; OTV: oseltamivir). Reproduced with permission from ref 195. Copyright 2016 American Chemical Society.

Generally, the cytotoxicity studies are not directed for a specific route by which MNPs-conjugates enter the body. Although some works show very interesting results in terms of cytotoxicity, more studies are needed before their therapeutic use.

8. Conclusion, challenges, and perspectives

This literature review aimed to survey the developed methods and respective results of the conjugation of MNPs with commercial antimicrobial drugs, including antibiotics, antifungals, and antivirals. It was verified that many metals and metal oxides had shown properties of high interest, namely as drug delivery systems, anticancer therapy and antimicrobial drugs. However, very few MNPs have been approved for clinical use by FDA and EMEA. Standards should be urgently developed to decrease the risk of toxicity of nanoparticles and the negative effects of exposure. The pharmacokinetics of the MNPs and the conjugates should be studied to induce high selectivity and reduce the accumulation in non-targeted cells.

A limited number of materials were considered in the preparation of conjugated agents. Thus, several possible combinations emerge and may be studied in future works. Also, several challenges arise in the methods for MNPs synthesis and surface functionalization. The environmental and safety component should be improved during the MNPs preparation.

Regarding the methods for MNPs conjugation, method A was the most used. In this method, the MNPs and antimicrobial agents are only stabilized by ionic interactions and/or the formation of chelates. The MNPs surface functionalization can be further explored since covalently bonded synergism is preferred to the simple physical adsorption to prevent leaching of the drug from the

nanoparticles. In most studies, the conjugation of MNPs and antimicrobial drugs are performed mainly by surface adsorption, where the covalent bonding rarely appears. Here, a limited number of reports exists, and these reports mostly focus on AuNPs. Furthermore, in most of the research works, the complete physicochemical characterization of conjugates is not available, making it difficult to associate the MNPs design with their antimicrobial effect. This is particularly grievous for works describing simple conjugation (method A).

MNPs per se possess interesting antimicrobial properties, but their conjugation with available agents tend to exhibit relevant advantages, especially by diminishing cytotoxicity.

The antimicrobial performance of the conjugates was challenging to compare due to the use of different evaluation methodologies. Thus, the calculation of the FIC in future works is recommended to allow the comparison and decision-making on the most improved conditions for synergy.

MNPs have been successfully combined with several antibiotic and antifungal molecules. Nevertheless, the combination of MNPs with antivirals remains extremely limited. Mechanistic studies of MNPs-conjugates are very limited. However, simultaneous action of MNPs and antimicrobial agents seems to represent an important strategy to circumvent pathogenic resistance and impede its establishment.

Regarding cytotoxicity, in most cases, the conjugation presented lower cytotoxicity than the individual agents, and it is possible to obtain practical antimicrobial effects with lower drug concentrations. Only more recent research works present cytotoxicity studies, and further investigation is needed to determine the optimal balance between effect and toxicity.

Finally, MNPs-conjugates presented several advantages: decreased the individual dosages of drugs, minimized the cytotoxicity and increased the spectrum of antimicrobial coverage.

Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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