Reduction of antibacterial toxicity through nanostructured carriers

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ABSTRACT
Bacterial resistance to antibiotics is a global health problem that needs to be resolved through the discovery of new therapeutic strategies. With the advancement of nanotechnology, new formulations have been tested for the ability to potentiate the action of antibiotics in traditional use by delivering more appropriate concentrations or reducing the toxicity of these drugs. In addition, the advent of nanotechnology allowed new strategies to be implemented to combat microbial resistance. The objective of this work was to carry out a bibliographic survey of the most recent formulations tested in nanotechnology to reduce the toxicity of antimicrobials, especially antibacterials, and/or increase their therapeutic effectiveness.

Keywords: Nanotechnology, Antibacterials, Toxicity.

1 INTRODUCTION

The emergence of pathogen species with genetic alterations that confer antibiotic resistance reaches a critical level, invalidating the main antimicrobial drugs currently used. According to the World Health Organization (WHO) research report, the main causes for antimicrobial resistance are long-term exposure to antimicrobial drugs, inappropriate use of medication by patients, abrupt withdrawal of the antibiotic, and the patient's genetic makeup (BELLOTTO et al., 2022).

The rapid increase of pathogenic microorganisms with antimicrobial-resistant profiles becomes a major global public health problem (NAINU *et al.*, 2021). Given this scenario, antimicrobial resistance has become a major challenge, and there is a need to develop new antibiotics with a much more prominent inhibitory effect on bacterial growth and with less toxicity (ENGIN; ENGIN, 2019). The rational use of antimicrobials is related to the maximization of their therapeutic effects and reduction of toxicity and antimicrobial resistance, seeking greater efficacy combined with lower toxicity (SINGH et al., 2020).

Currently, a change in the use of conventional antibiotics (GERA; KANKURI; Kogermann, 2021). The development of therapies based on nanoparticles and nanomaterials has become a fast-growing area in the field of nanotechnology, enabling the development of nanoantibiotics with multifunctional, targeted characteristics, vastly increased bactericidal efficiency, reduced toxicity, decreased adverse side effects, increased bioavailability, decreased dose, reduced concentrations of antibacterials, and the development of resistance antimicrobial (KUMAR; DAS, 2017).

In this context, nanobiotechnology represents an important resource in the fight against pathogens, as it was developed in a multidisciplinary field with a great potential in pharmaceutical applications, especially against hard-to-reach resistant microorganisms treatment such as bacteria (SOFI et al., 2022).

2 METHODOLOGY

This is an exploratory, descriptive and retrospective literature review on the toxicity of antimicrobials through the use of nanoformulations. According to Brasileiro (2016), the bibliographic review serves to recognize the unity and interpretive diversity existing in the thematic axis in which the problem under study is inserted, to expand, branch the interpretative analysis, as well as to compose the abstractions and syntheses that any research requires collaborating for the coherence in the researcher's argumentations.

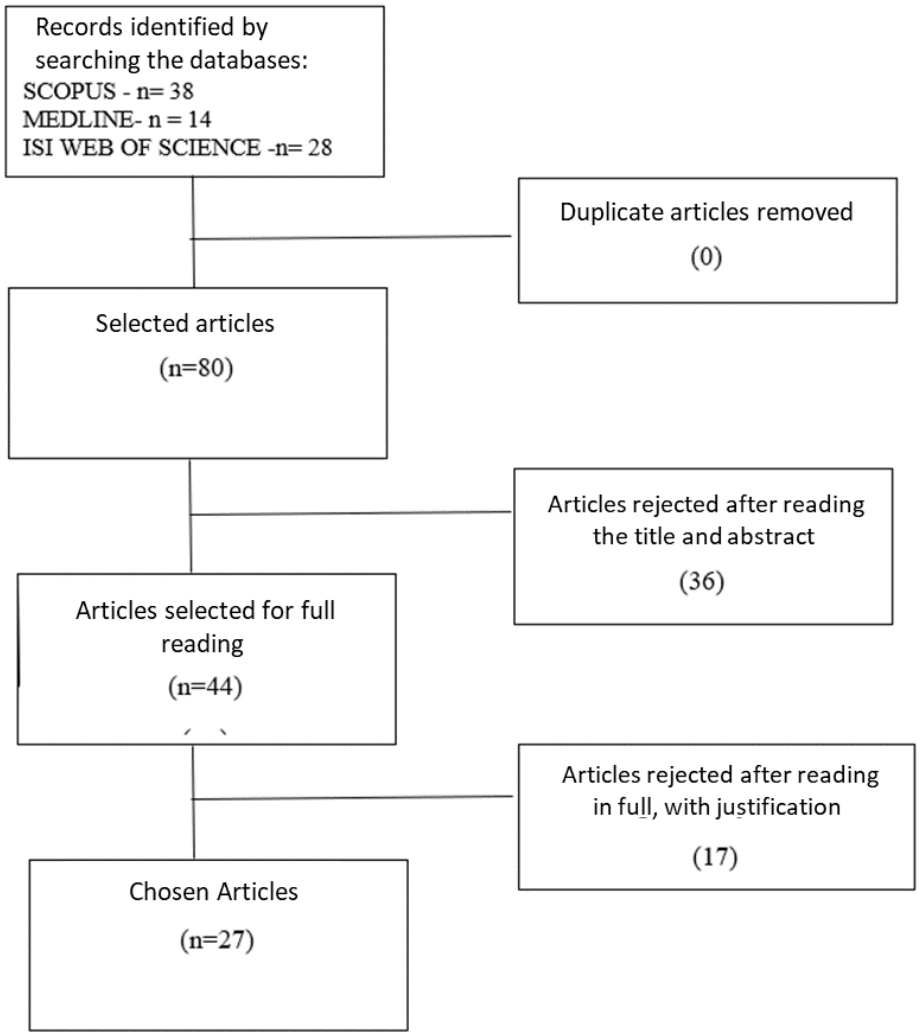
To survey the articles, online searches were performed in the databases Scopus, Medline and Web of Science through the Escritha platform. After choosing the database, the descriptors were selected, based on the standards established by the DeSC (Descriptors in Health Sciences), having as descriptors the following terms: nanotechnology, antimicrobials and toxicity (and their counterparts in English and Spanish). The search strategy used was based on the articulation with the Boolean operators (AND, OR, AND NOT).

The search for articles was conducted in the period of May 2022, by systematic process, on the title, abstract and keywords of all published articles. The research used as inclusion criteria: texts in Portuguese, English and Spanish and available in full in the period between 2017-2022 and that had the use of antimicrobials. In addition, exclusion criteria were used: texts that were not related to the theme or that present duplicates and research on antimicrobials associated with another theme.

3 RESULTS AND DISCUSSION

When using the descriptors in the three databases, a total of 80 articles were found (Figure 1), and after a filtering process using the inclusion and exclusion criteria mentioned above, a final result of 27 articles were selected (Table 1).

Figure 1. Histogram of selection of articles.



Source: Own author.

3.1 NANOFORMULATIONS APPLIED TO ANTIMICROBIALS OF TRADITIONAL USE

Some studies have focused efforts on finding new formulations of antimicrobials that are already used in therapy traditionally, in order to improve their therapeutic effectiveness or decrease the toxicity of these drugs through the use of nanoformulations. These studies present the advantage of extensive knowledge about these drugs and their good clinical acceptability, proposing only a more modern formulation that delivers greater efficacy compared to traditional formulations. The following are some of these studies and their main results.

3.2 GOLD NANOPARTICLES LOADED WITH CIPROFLOXACIN

Ciprofloxacin is a second-generation fluoroquinolone with a broad microbial spectrum. Used in the clinic to fight a number of urinary tract and gastrointestinal infections, because it has activity against various microorganisms. One study focused on the synthesis and physical characterization of Ciprofloxacin-laden gold nanoparticles (CIP-AuNPs) and their effect on the colonization of

Enterococcus faecalis in the liver and kidneys of mice. The nanoparticles produced were stable and exerted increased in vitro antibacterial activity against *E. faecalis* compared to free ciprofloxacin, demonstrating to be a promising therapeutic alternative. In addition, the nanoformulation containing ciprofloxacin showed less ability to generate hemolytic anemia than free ciprofloxacin since the dose used was less than 20ug (280ug for free ciprofloxacin and 14ug for the nanoparticle (NAWAZ et al., 2021).

3.3 MESOPOROUS SILICA NANOPARTICLES FUNCTIONALIZED WITH CLARITHROMYCIN

Another study investigated systems with the potential to improve drug efficacy through mesoporous silica nanoparticles. In this study, Clarithromycin was used, an antimicrobial of the macrolide class that has activity against gram-positive cocci and acts by inhibiting protein synthesis. The results showed that the nanosystems loaded with clarithromycin against *Staphylococcus aureus* and *Escherichia coli* improved the performance of the antimicrobial activity of this drug, reducing the minimum inhibitory concentration by 5 times when compared to the free formulation. Histological studies have also pointed out that the drug generated a greater accumulation in the liver and kidneys and notably in the lung tissue, increasing the possibility of microbial infection therapy, especially in respiratory infections (KHOSRAVIAN et al., 2018).

3.4 MAGNETITE/SILVER NANOPARTICLES WITH ADSORBED RIFAMPICIN

Rifampicin is an antimicrobial with limited use today, being used mainly in mycobacterial infections and skin infections. One of the main limitations of its use is due to the large occurrence of drug interactions since this drug is a strong inducer of liver enzymes. In one study, nanoparticles of magnetite with silver were used in order to improve the adsorption of the antibiotic rifampicin as well as its antibacterial properties. The rifampicin molecules on the surface in the nanoparticle extended the spectrum of antimicrobial activity for strains of *Pseudomonas fluorescens* and *Bacillus pumiluse* for which the nanoparticle without rifampicin showed no activity, in addition to forming a microbial inhibition halo 2 times larger for the conjugated nanoparticle. The evaluation of cytotoxicity showed no harmful action in normal human fibroblasts, while the effect on the viability of human kidney embryonic cells was dependent on time and dose (IVASHCHENKO et al., 2017).

3.5 POLYDOPAMINE-AMINOGLYCOSIDE NANOCONJUGATES

Dopamine, which presents itself as a neurotransmitter in the human brain serving as a messenger and handles behavioral responses, provided an ideal platform through self-polymerization under aerobic conditions leading to the formation of a beneficial organic biopolymer, polydopamine

(PDA). This polymer can be used to attach ligands containing amine or thiol to obtain conjugates. One study used autopolymerized polydopamine nanoparticles bound to aminoglycosides (Gentamicin, Canamycin, and Neomycin) through amino portions to obtain nanoconjugates with these antimicrobials. Of these three nanoconjugates, the nanoconjugate containing kanamycin exhibited the highest activity against potent pathogens, lowest toxicity in human embryonic kidney cells (HEK 293) and intense toxic effects in human glioblastoma cells (U87). Together, these results support the promising potential of these nanoconjugates to be used as potent antimicrobials in future applications. (SINGH et al., 2020)

3.6 NEW ANTIMICROBIALS IN DEVELOPMENT

In recent years, antimicrobial peptides have had a renaissance as the world currently faces an emergency in terms of serious infections escaping antibiotic treatment. Covalent conjugation with polymers is an interesting strategy to modulate the pharmacokinetic profile of antimicrobial peptides and increase their biocompatibility profile. It can also be an effective approach to develop active coatings for implants and medical devices and prevent biofilm formation on their surface (BELLOTTO et al., 2022).

Engineered nanoparticles have been intensively studied over the past decade for use in environmental purifications, energy storage/conversion, antimicrobial coating agents, and so on. Various monometallic and doped nanomaterials have been prepared and tested for photocatalysis and antimicrobial toxicity. Nanoparticles are of interest as antibacterial agents and later as anti-coating materials due to their large surface area relative to volume and the generation of highly reactive oxygen species that are the main agents known to damage the cell wall of many microbes. Many studies have investigated the antibacterial effect of monometallic and doped nanomaterials. *Bacillus subtillis* (gram positive) and *Escherichia coli* (gram negative) were taken as model microbes for antibacterial tests using different engineered nanoparticles (SWAMINATHAN; SHARMA, 2019).

Table 1. Extraction of data from articles and organized according to the extracted database.

Article Title	Database	Main Results	Reference
Polymer Conjugates of Antimicrobial Peptides (AMPs) with D-Amino Acids (D-aa): State of the Art and Future Opportunities	Scopus	Covalent conjugation with polymers modulates the pharmacokinetic profile of antimicrobial peptides and increases their biocompatibility profile	BELLOTTO et al., 2022
An overview of antimicrobial and anticancer potential of silver nanoparticles	Scopus	Antimicrobial and anticancer properties of silver nanoparticles. Applications in biomedical devices, implants and environmental remediation	ABASS SOFI et al., 2022
Antimicrobial activity of the engineered nanoparticles used as coating agents	Scopus	Nanocoatings control the growth of microbes and oxidize certain common indoor air pollutants, such as VOCs and NOx.	SWAMINATHAN; SHARMA, 2019
Antimicrobial peptide delivery: An emerging therapeutic for the treatment of burn and wounds	Scopus	Antimicrobial peptides are effective in treating wounds and burns, along with minimal chances of developing resistance	JAVIA *et al.*, 2018
A Novel Polymeric Nanohybrid Antimicrobial Engineered by Antimicrobial Peptide MccJ25 and y Activities	Scopus	Polymeric nanoparticles have excellent bactericidal activity against *E. coli*	HAITAO *et al.*, 2022
Pharmaceutical approaches to antimicrobial resistance: prospects and challenges	Scopus	Natural antibacterial compounds are effective against antimicrobial resistance	NAINU *et al.*, 2021
Bio-mediated silver nanoparticle synthesis: mechanism and microbial inactivation	Scopus	The silver nanoparticles exhibited good E. *coli* inactivation due to the participation of free radicals as evidenced by electron spin resonance spectroscopy	CHAKRABORTY *et al.*, 2017
Anti-algae efficacy of silver nanoparticles to Microcystis aeruginosa: Influence of NOM, divalent cations, and Ph	Scopus	Direct contact of silver nanoparticles with algae cells and the release of silver ions contributed to the anti-algae capacity of the nanomaterial	HUANG *et al.*, 2016
In vitro toxicity, apoptosis and antimicrobial effects of phyto-mediated copper oxide nanoparticles	Scopus	Copper oxide nanoparticles are highly stable, spherical and safe. Its application can be expanded as antimicrobial and anticancer agents	GOPINATH *et al.*, 2016
Antimicrobial peptides - Unleashing their therapeutic potential using nanotechnology.	Medline	Delivery of AMPs employing nanotechnological approaches avoids instability and toxicity, and provides a controlled delivery profile and prolonged, antimicrobial activity	GERA; KANKURI; KOGERMANN, 2021
Antimicrobial properties of nanoparticles in the context of advantages and potential risks of their use.	Medline	The nanoparticles present antimicrobial potential through multifaceted mechanisms, have increased surface area, which improves their chemical reactivity and mobility.	STARON; DLUGOSZ, 2021

Nanoantibiotics: A Novel Rational Approach to Antibiotic Resistant Infections.	Medline	The drug administered via a nanoparticle transporter has a much more prominent inhibitory effect on bacterial growth and drug toxicity, along with prolonged drug release	ENGIN; ENGIN, 2019
Lipid-Based Antimicrobial Delivery-Systems for the Treatment of Bacterial Infections.	Medline	The protection against the deactivation of antibiotics in liposomal nanocarriers and their fusogenicity constitute the greatest advantage of liposomal antimicrobial carriers over free antimicrobials in solution	WANG *et al*., 2019
Therapeutic Nanotechnology for Bone Infection Treatment - State of the Art.	Medline	Nanoantimicrobials designed to have controlled and sustained drug release kinetics, surface modifications, and increased affinity for biofilms	GUO; XUE; WONG, 2018
Emerging nanotechnology based strategies for diagnosis and therapeutics of urinary tract infections: A review.	Medline	Nanoparticles are beneficial in terms of decreasing toxicity, prevailing over resistance and lowering costs	KUMAR; DAS, 2017
Polydopamine -aminoglycoside nanoconjugates: Synthesis, characterization, antimicrobial evaluation and cytocompatibility	Web of Science	Polydopamine has antimicrobial activity and properties such as biodegradability, biocompatibility, development of low resistance, high efficacy, low cytotoxicity	SINGH *et al*., 2020
Enhancement Antimicrobial Activity of Clarithromycin by Amine Functionalized Mesoporous Silica Nanoparticles as Drug Delivery System	Web of Science	The mesoporous silica nanoparticles have antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*, good payload and pH sensitive drug release kinetics	KHOSRAVIAN *et al*., 2018
Nanotechnological strategies for systemic microbial infections treatment	Web of Science	Several drug delivery systems based on nanotechnology can contribute to the biological performance of active substances for the treatment of microbial diseases triggered by fungi, bacteria, viruses and parasites	DOS SANTOS RAMOS *et al*., 2020
Influence of silver content on rifampicin adsorptivity for magnetite/Ag/rifampicin nanoparticles	Web of Science	The results show that 5%-10% of the silver content in magnetite/Ag NPs is already sufficient for antimicrobial properties against *Streptococcus salivarius* and *Staphylococcus aureus*	IVASHCHENKO *et al*., 2017
Cytotoxicity and antimicrobial efficiency of selenium nanoparticles biosynthesized bySpirulina platensis	Web of Science	Biogenic SeNPs showed potential antimicrobial activity against gram-negative bacteria and yeast-like fungi *C. albicans* ATCC10231	ABBAS; ABOU BAKER; AHMED, 2021
Ciprofloxacin-Loaded Gold Nanoparticles against Antimicrobial Resistance: An In Vivo Assessment	Web of Science	CIP-AuNPs are promising and biocompatible therapeutic alternatives for infections induced by E.-*faecalis* resistant to conventional drugs (e.g., beta-lactams and vancomycin)	NAWAZ *et al*., 2021

Preparation and in Vitro Antimicrobial Activity of Silver-Bearing Degradable Polymeric Nanoparticles of Polyphosphoester-block-Poly(L-lactide)	Web of Science	The packaging of silver carbene complexes (SCCs) in the delivery system based on degradable polymeric nanoparticles improved the minimum inhibitory concentrations up to 70%, compared to SCCs alone in	LIM, *et al*., 2015
Evaluating the antimicrobial activity and cytotoxicity of polydopamine capped silver and silver/polydopamine core-shell nanocomposites	Web of Science	Ag-PDA nanocomposites showed negligible toxicity to human embryonic kidney cells (HEK-293T) and human dermal fibroblasts (HDF) and excellent antimicrobial activity	SHUMBULA *et al*., 2022
Polymeric nanoparticles in development for treatment of pulmonary infectious diseases	Web of Science	Polymeric nanoparticles with direct delivery to lungs loaded with antimicrobials, minimizing systemic exposure to therapeutic agents	LIM, *et al*., 2016
Prevention of motile Aeromonas septicemia in Nile tilapia, Oreochromis niloticus, using thyme essential oil and its nano-emlusion	Web of Science	The nanoemulsion of dietary thyme essential oil showed antibacterial activity	SALAM *et al*., 2021
Supramolecular amphiphiles of Beta-cyclodextrin and Oleylamine for enhancement of vancomycin delivery	Web of Science	In vitro antibacterial testing showed that BCD-OLA had a 2- and 4-fold lower MIC against methicillin-resistant Staphylococcus aureus (SA) and methicillin-resistant Staphylococcus aureus (MRSA), respectively, compared to pure vancomycin.	SALIH *et al*., 2020
Silver Nanoparticle-Induced Autophagic-Lysosomal Disruption and NLRP3-Inflammasome Activation in HepG2 Cells Is Size-Dependent	Web of Science	The results indicate the potential of 10 nm AgNPs encompassed in the vesicle to induce cytotoxicity by a mechanism involving disturbances in the autophagy-lysosomal system and inflammasome activation	MISHRA *et al*., 2016

Source: Own author

4 FINAL CONSIDERATIONS

Antibacterials continue to be a strategy in current pharmacological treatments, but they are not exempt from adverse reactions or often become ineffective, mainly for bacteria. Antibiotic resistance is a problem that has been constantly alerted by the WHO and that needs urgent solutions.

Nanobiotechnology presents itself today as a great strategy in combating pathogens, as the great potential of nanoparticles in pharmaceutical applications enables the development of nanoantibiotics with multifunctional, targeted characteristics, greatly increased bactericidal efficiency and fewer adverse effects. Some studies have concentrated efforts on finding new nanomolecular formulations of antimicrobials that are already used in traditional therapy.

Studies show that nanoparticles act by protecting the antibiotic against aggressive agents, which promote greater activity against potent pathogens, less toxicity in cells and less toxic effects. These

results corroborate the promising potential of these nanoparticles to be used as potent antimicrobials in future applications and help and resolve a number of pathologies in different areas of health.

The approaches in the use of nanoparticles can be multiple, being an excellent tool to overcome bacterial barriers and to induce low capacity in the development of resistance varieties

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