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SILVER NANOPARTICLES AGAINST STAPHYLOCOCCUS AUREUS RESISTANT TO METICILLIN: A LITERATURE REVIEW

NANOPARTÍCULAS DE PRATA CONTRA STAPHYLOCOCCUS AUREUS RESISTENTE À METICILINA: UMA REVISÃO DE LITERATURA

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ABSTRACT

The Methicillin-resistant Staphylococcus aureus (MRSA) represents a critic risk to public health because it has resistance to multiple antimicrobial agents and is one of the most common nosocomial pathogens. Consequently, researches to develop or modify antimicrobial compounds to improve bactericidal against the potential strains of MRSA have been grouwing. In this context, this study aimed to conduct a literature review about the antimicrobial activity against MRSA of silver nanoparticles (AgNPs) and discuss the main results. The survey was conducted in the ScienceDirect database, where the descriptors used were “silver nano * and MRSA”. Based on the results, we can conclude that the antimicrobial effects of the AgNPs against MRSA are promising in several areas, as these did not cause damage to healthy cells and caused no observable side effects.

Keywords: antibacterial activity, MRSA, nanotechnology.

RESUMO

O Staphylococcus aureus resistente à meticilina (MRSA) representa um grande risco à saúde pública, pois possui resistência a múltiplos agentes antimicrobianos e é um dos patógenos nosocomiais mais comuns. Consequentemente, vem crescendo as pesquisas com finalidade de desenvolver ou modificar compostos antimicrobianos visando a melhoria do potencial bactericida contra as cepas de MRSA. Neste contexto, este estudo teve como objetivo realizar uma revisão de leitura sobre a atividade antimicrobiana contra MRSA das nanopartículas de prata (AgNPs) e discutir os principais resultados encontrados. A pesquisa foi realizada na base de dados ScienceDirect, onde os descritores utilizados foram “silver nano and MRSA”. Baseado nos resultados encontrados, podemos concluir que os efeitos antimicrobianos das AgNPs contra MRSA são promissores em diversas áreas, uma vez que estas não causaram danos às células saudáveis e não provocaram efeitos colaterais observáveis.*

Palavras-chave: *atividade antibacteriana, MRSA, nanotecnologia.*

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INTRODUCTION

Silver (Ag) has been used in the form of metallic silver, silver nitrate, silver sulfadiazine for the treatment of burns, wounds and various bacterial infections. But with the advent of various antibiotics, the use of these silver compounds has been markedly reduced (RAI *et al.*, 2009).

Nanotechnology is gaining more and more notoriety due to its ability to modulate metals to their nanometric size, which dramatically alters the chemical, physical and optical properties of metals. Among nanotechnology products, there is a great interest in the use of silver nanoparticles (AgNPs), which stand out for their excellent antimicrobial activity. Among its properties, it presents good conductivity, great catalytic effect and high surface area. In addition, it has good thermal stability and is stable to UV/Visible radiation (COWAN *et al.*, 2003).

AgNPs have been used in various forms, whether in cosmetics, drugs and biosensors (ASHARANI *et al.*, 2008). There is a possibility of numerous uses, including: dressings, inside refrigerators, to delay food spoilage, antimicrobial insoles, to avoid odors, air purifiers and surgical instruments (SOUSA, 2013). Since the 1960s, following the advent of penicillin, *Staphylococcus aureus* has been a major concern within the approach to antibiotic resistance. MRSA is a term used to describe strains of *S. aureus*, an aerobic gram-positive bacterium with acquired resistance to β-lactam antibiotics such as methicillin, oxacillin, and cephalosporins. It is among the most common pathogens that cause nosocomial infection (HENA; SUDHA, 2011). MRSA strains are divided into two types: Hospital-Acquired MRSA (MRSA-HA from Healthcare-Acquired), isolated mainly from hospitalized patients, and Community-Acquired MRSA (MRSA-CA from Community-Acquired) from outpatients (MEDIAVILLA *et al.*, 2012).

Whereas an individual is infected by antibiotic resistant bacteria, their stay in hospital is prolonged and requires multiple treatment of broad spectrum antibiotics, which are less effective, more toxic and more expensive (WEBB *et al.*, 2005). Nanotechnology provides a good platform on? modifying and developing the important properties of AgNPs, in particular for solving the problem of the emergence of antibiotic resistant bacteria (GEMMELL *et al.* 2006).

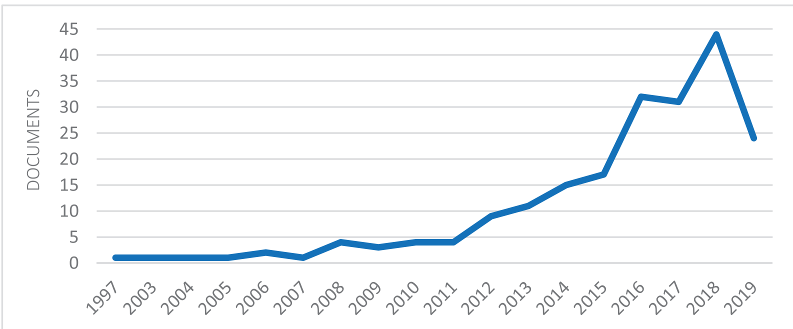
Silver annihilates over 650 pathogens and does not create resistance (ANTUNES *et al.*, 2013) and these effects can be increased when silver is at its nanometer size due to its high surface area and unique chemical and physical properties (KIM *et al.*, 2007). AgNPs in the 10-100 nm range showed strong bactericidal potential against gram-positive and gram-negative bacteria. This is because, when it comes into contact with the cell membrane of these microorganisms, AgNPs cause damage to the cellular respiration process and permeability. In addition, AgNPs bind to sulfur and phosphorus present in DNA, preventing cell division (MORONES *et al.*, 2005). The effectiveness of silver nanoparticles is due to their action on various bacterial components, unlike the common mechanistic action of antibiotics (MATAI *et al.*, 2014).

Therefore, the importance of research is evidenced in order to develop or modify antimicrobial compounds to improve bactericidal potential, especially against MRSA strains, which is a priority area of research, is evident. In this context, the present work aims to perform a literature review of studies related to the bactericidal activity of AgNPs against pathogenic MRSA strains.

MATERIAL AND METHODS

This study is a review of the literature conducted between August 2018 and April 2019 in the ScienceDirect database. The research in the database has been delimited for search articles using the following keywords: Silver nano* and MRSA. Were found 205 articles using these descriptors as shown in the graph in Figure 1. Among the documents found, many of them were excluded because they are chapters of books,are associated with antibiotics, antiparasitic drugs or because they do not specifically address silver nanoparticles and the MRSA bacterium. The remaining 22 articles were used in this review because they were articles of research whose theme was related to this study.

Figure 1 - Documents found on the ScienceDirect using the descriptors "silver nano* and MRSA" and their respective years.



Source: Science Direct.

RESULTS AND DISCUSSIONS

Table 1 shows a summary of the articles selected in the ScienceDirect database to carry out the review.

Table 1 - List of articles used in the study.

Title	Reference
Wound-dressing materials with antibacterial activity from electrospun gelatin fiber mats containing silver nanoparticles	RUJITANAROJ; PIMPHA; SUPAPHOL, 2008
The use of BMP-2 coupled - Nanosilver - PLGA composite grafts to induce bone repair in grossly infected segmental defects	ZHENG *et al.*, 2010
Chitosan-hyaluronic acid/nano silver composite sponges for drug resistant bacteria infected diabetic wounds	ANISHA *et al.*, 2013
Pluronic-coated silver nanoprisms: Synthesis, characterization and their antibacterial activity	MARTA *et al.*, 2014

Substrate independent silver nanoparticle based antibacterial coatings	TAHERI *et al.*, 2014
Antimicrobial activity of TiO_2:Ag nanocrystalline heterostructures: Experimental and theoretical insights	ANDRÉ *et al.*, 2015
Designing chitosan-silver nanoparticles-graphene oxide nanohybrids with enhanced antibacterial activity against *Staphylococcus aureus*	MARTA *et al.*, 2015
Green and ecofriendly synthesis of silver nanoparticles: Characterization, biocompatibility studies and gel formulation for treatment of infections in burns	JADHAV *et al.*, 2016
Controlled assembly of silver nano-fluid in *Heliotropium crispum* extract: A potent anti-biofilm and bactericidal Formulation	KHAN *et al.*, 2016
Silver ion doped ceramic nano-powder coated nails prevent infection in open fractures: In vivo study	KOSE *et al.*, 2016
Strontium (Sr) and silver (Ag) loaded nanotubular structures with combined osteoinductive and antimicrobial activities	CHENG *et al.*, 2016
Biocidal mechanism of green synthesized thyme loaded silver nanoparticles (GTAgNPs) against immune evading tricky methicillin-resistant *Staphylococcus aureus* 090 (MRSA090) at a homeostatic environment	MANUKUMAR *et al.*, 2017
Efficacy of silver nanoparticles mediated by *Jania rubens* and *Sargassum dentifolium macroalgae*; Characterization and biomedical applications	SABER *et al.*, 2017
Hydrogels incorporated with silver nanocolloids prepared from antioxidant rich *Aerva javanica* as disruptive agents against burn wound infections	HASHMI *et al.*, 2017
Selective laser melting porous metallic implants with immobilized silver nanoparticles kill and prevent biofilm formation by methicillin-resistant *Staphylococcus aureus*	INGMAR *et al.*, 2017
Chemical synthesis and characterization of chitosan/silver nanocomposites films and their potential antibacterial activity	SHAH; HUSSAIN; MURTAZA, 2018
Development and characterisation of furcellaran-gelatin films containing SeNPs and AgNPs that have antimicrobial activity	JAMRÓZ *et al.*, 2018
Formulation Optimization of Chitosan-Stabilized Silver Nanoparticles Using In Vitro Antimicrobial Assay	PANSARA *et al.*, 2018
ROS mediated destruction of cell membrane, growth and biofilms of human bacterial pathogens by stable metallic AgNPs functionalized from bell pepper extract and quercetin	AHMED *et al.*, 2018
Synthesis of $Ag@Fe_2O_3$ nanocomposite based on O-carboxymethylchitosan with antimicrobial activity	DEMARCHI *et al.*, 2018
Synthesis, characterization and antibacterial activity of silverdoped TiO_2 nanotubes	AYDIN *et al.*, 2018
Silver-nanoparticles increase bactericidal activity and radical oxygen responses against bacterial pathogens in human osteoclasts	AURORE *et al.*, 2018

Source: Authors' construction.

The bone morphogenetic protein 2 (BMP-2) is an osteoinductive used for treatment of many bone fractures and bone defects, for this reason, Zheng *et al.* (2010) manufatured BMP-2 coupled AgNPs- Poly(lactic-co-glycolic acid) composite bone grafts. The grafts were tested for 12 weeks on wounds infected with clinical strains of vancomycin resistant MRSA (strain Mu50, ATCC 700699). During this period there was no evidence of residual bacteria, thus demonstrating that AgNP is an effective antimicrobial that is non-toxic, and does not interfere with BMP-2 induced bone formation. In addition, it was found that the efficacy of AgNP is dose dependent and that the even higher silver concentrations provide more potent antibacterial activity.

André *et al.* (2015) conducted the first report on the effect of silver decorated titanium dioxide (TiO_2: Ag) NPs produced via hydrothermal treatment assisted by microwave irradiation, on *Candida spp* and MRSA biofilm. These NPs exhibited physicochemical properties that conferred antimicrobial activity against the pathogens tested. In a similar study, Aydin *et al.* (2018) synthesized one-dimensional

TiO2 nanotubes doped with Ag (5%) by the same method and tested their antimicrobial activity against three strains of gram-positive *Staphylococcus aureus (S. aureus)* (NRLL B-767, methicillin resistant 3, methicillin resistant 47). This study shows, all of the S. aureus strains exhibited identical sensitivity to TiO2: Ag nanotubes, and thus found that the material have great promise as effective antimicrobial reagent free of resistance.

Marta *et al.* (2015) manufacture nanocomposites of chitosan-AgNPs-graphene oxide nanohybrids to combine the strong antibacterial effect of AgNPs was combined with GO sheets' abilities to provide a scaffold structure for AgNPs and chitosan adsorption properties to maximize the interaction with MRSA cells through a capturing-killing process. The results found suggest a clear synergy between the three nanocomposite components, expressed by a better bacteriostatic and bactericidal effect against two MRSA strains (UCLA8076 and 1190R) than any single component or any two of them together.

Recently, Pansara *et al.* (2018) stabilized AgNP with chitosan (CH) at a ratio of 1: 4 to evaluate the minimum inhibitory concentration and minimal bactericidal concentration against MRSA. Both CH-AgNP concentrations, when compared with pure AgNP, were 4 to 14 times lower against MRSA isolates. In another study, Shah *et al.* (2018) also made CH-AgNPs to test antimicrobial activity in *S. aureus*, *Pseudomonas aeruginosa* (*P. aeruginosa*) and clinically isolated MRSA strains. These authors reported that when compared with commercially available dressings (Aquacel Ag®, Bactigras® and Kaltostat®), CH-AgNPs were equally or more effective than them.

In Rujitanaroj *et al.* (2008), ultrafine gelatin fibers (22% w / v in 70 vol% acetic acid) containing 2.5% wt% $AgNO_3$ are proposed for use as antibacterial dressings in burn wounds. AgNP first appeared in the solution after it had been aged for at least 12 h, with the amount of AgNP formed increasing with increasing aging time. According to the results obtained, the pure fibers showed no activity against the tested bacteria. Whereas the fibers AgNPs-containing, egardless of the sample type, showed higher activity against *P. aeroginosa* strain, followed by *S. aureus*, *E. coli* and MRSA, respectively.

Jadhav *et al.* (2016) evaluated the effect of AgNPs against organisms involved infections associated with burns (*P. aeruginosa*, *S. aureus* and MRSA). The AgNP used were synthesized by treatment of silver nitrate with aqueous plant extract *Amania baccifera*, forming a gel with a concentration of 0.025%. The comparative bactericidal efficacy of the synthesized gel and commercialized formulation marked ionic Silverex ™ (silver nitrato gel 0.2% w / w) showed equal zone of inhibition against all pathogenic bacteria. The formulated AgNPs gel consisting of 95% lower silver concentration compared to marketed formulation was equally effective against all organisms. Therefore, these authors reported that the gel could serve as an effective and better alternative tropical antimicrobial in antibiotic resistant genotypes for treatment of infections in burns.

In another study related to burn infections, Hashmi *et al.* (2017) synthesized AgNPs from the antioxidant-rich aqueous extract of *Aerva javanica* which after incorporation into chitosan hydrogels were applied topically to partial thickness burn infections (2 × 10 CFUs from MRSA and *P. aeruginosa*) raised in albino mice (Balb / W) . s. The results showed in a significant reduction in infection and healing time. Recently, in Ahmed *et al.* (2018) silver nanoparticles was synthesized mediated by enzyme β galactosidase, resulting in NPs in the 6 to 16 nm range that also demonstrated good antibacterial activity against MRSA, *Escherichia coli* (*E. coli*), *P. aeruginosa* and *S. epidermidis*.

AgNP has also been applied as a dressing for diabetic ulcers, as in Anisha *et al.* (2013) who developed an antimicrobial sponge composed of chitosan, hyaluronic acid and AgNP. Prepared sponges showed potent antimicrobial properties against various types of strains tested and at higher concentrations of AgNP showed antibacterial activity against MRSA. In addition, the results showed that higher concentrations of AgNP lead to lower cell viability and, therefore, the authors suggest that if the optimal concentration of AgNP in the nanocomposite to cause less toxic antibacterial action, this sponge will be useful for treatment proposed.

Heliotropium crispum (HC) extract can also be used in the synthesis of AgNPs, as seen in Khan *et al.* (2016). They evaluated the antimicrobial and anti-biofilm properties of biologically synthesized AgNPs in clinical isolates of MRSA, *P. aeruginosa* and *Acinetobacter baumannii*. In the study, all bacterial pathogens tested against HC-AgNPs were susceptible, suggesting an efficient use of Ag nanocomposites to address the emerging issue of multiple drug resistance in bacterial strains. In addition, the results implied that 40 nm AgNPs exhibit a potent bactericidal response through cell wall destruction. Thus, they concluded that products loaded with HC-AgNPs could control several drug resistant pathogens in the future.

Saber *et al.* (2017), in turn, used as aqueous extracts *Jania rubens* and *Sargassum dentifolium* to synthesize AgNPs. These at concentrations of 10 4 - 10 5 / mL were sufficient against the pathogens *Salmonella typhimurium, Enterobacter aerogenes, P. aeruginosa*, E. coli and MRSA. In addition, biofilm formation results implied significant inhibition at the onset of the adherence stage at various concentrations of tested AgNPs, indicating that they can be an effective antimicrobial agent without causing microbial resistance even after long term use. The bactericidal effects of AgNPs have also been investigated by Aurore *et al.* (2018) in human osteoclasts infected with MRSA and non-virulent E. coli. In this study, they noted that treatment with AgNPs at a non-toxic concentration induces bactericidal activity and generation of reactive oxygen species in osteoclasts, regardless of the direct toxicity of silver, significantly increasing bactericidal activity against the studied pathogens.

Marta *et al.* (2014) investigated the antibacterial efficiency of AgNP coated with pluronic, synthetic block copolymer consisting of PEO (poly (ethylene oxide)) - PPO (poly (propylene oxide)) - PEO (poly (oxide oxide)) chains ethylene)) against two strains of MRSA (UCLA 8076 and 1190R) using triangular shaped nanoparticles (nanoprisms) instead of commonly exploited spherical NPs. The strong antibacterial activity found against MRSA strains was explained considering that triangular nanoprisms exhibit higher reactivity crystalline facets and presumably a higher rate of ion release from their tips and edges compared to other forms of NPs. In addition, the results indicated that

Ag nanoprisms exhibit antibacterial activity in different ways depending on their size. While small nanoprisms interact more efficiently with the bacterial surface, the larger ones promote the release of silver ions due to the high surface energy that makes them chemically less stable.

Kose *et al.* (2016) developed Ag-ion-doped calcium phosphate-based ceramic NPs as an implant coating to provide biocompatibility and antibacterial activity. The in vivo study in rabbits was performed in 3 situations: uncoated implant, hydroxyapatite coated implant and silver doped hydroxyapatite coated implant. Prior to implantation, 50μl of solution containing 106 colony forming unit (CFU) / mL MRSA was injected into the rabbit intramedullary canal, which was monitored for 10 weeks. Microbiological results showed that less bacterial growth was detected when using silver-doped ceramic coated implants compared with the other two groups ($p = 0.003$). As well, no cellular inflammation and toxic effects were observed around Ag coated prostheses. Therefore, it has been shown that the proposed coating can prevent bacterial colonization and MRSA infection in exposed fractures compared to implants without any coating.

In Ingmar *et al.* (2017), selective laser fusion (SLM) implants were biofunctionalized by incorporation of AgNPs into a grown oxide surface layer using plasma electrolytic oxidation (PEO) in Ca / P-based electrolytes. Antimicrobial assays consistently showed strong antimicrobial activity of implants developed against MRSA including released activity, surface antimicrobial activity, and prevention of biofilm formation. In addition, porous implants showed four times greater release of Ag ions, twice greater inhibition zones, and an additional order of magnitude reduction in CFU number in the ex vivo antimicrobial assay compared to similarly sized solid implants. the PEO. Based on these data, the authors considered promising new implants to develop an additional (preclinical) clinician. Similar results against MRSA were found in Cheng *et al.* (2016), where Ti implant surfaces were anodized and hydrothermally treated to deposit strontium (Sr) and Ag loaded nanotube coatings.

Manukumar *et al.* (2017) synthesized green thyme-loaded AgNPs (GTAgNPs) and first tested their effectiveness on MRSA090. Green thyme (*Thymus vulgaris*) was chosen because it has a substance called thymol, which is capable of killing bacteria by destabilizing the bacterial membrane. In this study, they found that 75 nm NP has strong antimicrobial properties, cell leakage, potassium flux and antibiofilm. As well as, it had a great effect disintegrating the plasma membrane of MRSA090, whose minimum inhibitory concentration was 1mg / mL, stimulating the release of cellular materials. In addition, they were effective against MRSA biofilm and showed significant anti-cancer properties in breast and lung cancer strains. Based on this, the authors strongly suggested that drugs designed with GTAgNPs active molecules could be successfully used against MRSA infections in the future.

Demarchi *et al.* (2018) manufacture magnetic nanocomposite via reduction of $AgNO_3$ by $NaBH_4$, sucrose or without reducing agent in a suspension containing O-carboxymethylchitosan and γFe_2O_3. The particle produced without reducing agent was the most effective against pathogens, revealing its antimicrobial activity in *S. aureus, E. coli, Candida albicans* and MRSA. Following the same line of research, Taheri *et al.* (2014) developed AgNP based antibacterial coatings with an average diameter of 11 nm, which show excellent antibacterial efficacy against MRSA, *S. epidermidis* and *P. aeruginosa* strains, as well as a good profile of biocompatibility of mammalian cells. Furthermore, they studied the effect of the coatings on the innate immune response in culture primary macrophage and found that natural innate immune inflammatory processes cannot be negatively altered, thus making the material interesting for medical device application.

Jamróz *et al.* (2018) were the first to explore the antimicrobial properties of furcellarangelatin (FUR / GEL) films incorporated with selenium nanoparticles (SeNPs) and AgNPs. In this study, films loaded with SeNPs exhibited antibacterial performance against E. coli, S. aureus and MRSA. However, the antibacterial activity of FUR / GEL films with AgNPs was not effective. These, even applied in various concentrations did not show any antimicrobial activity against S. aureus and MRSA, only the films with highest concentration of Ag (10% and 15%) showed inhibition zones against E. coli (9 mm and 10 mm, respectively).

Based on the studies analyzed, it was found that only the latter was unsuccessful in eradicating bacteria resistant to multiple antibiotics. Therefore, we can conclude that in most cases, when using AgNPs combined with other materials, they showed a significant increase in their antimicrobial activity against MRSA and other pathogens tested.

CONCLUSION

The results found in the literature allow us to infer that the antimicrobial effects of AgNPs are attributed to the dose, form of NP and various mechanisms of action, as well as disruption of cell morphology, generation of reactive oxygen species, modulation of cell signaling and action against the strains of MRSA. In addition, formulations with AgNPs as compared to commercial products were less toxic and equally or more effective against the MRSA pathogen. These data indicate a wide range of pharmacological properties for AgNPs, proving antimicrobial activities that can be used not only for MRSA strains, but also for other promising therapeutic actions such as implant coatings and wound and burn infection treatments.

Finally, it is hoped that these results will contribute to the orientation of new studies on the AgNPs in the eradication of multiple antibiotic resistant bacteria of public health importance, directing the research to other areas not yet explored. It is emphasized that further i*n vivo* studies are needed to validate the reported observations and follow up on studies targeting clinical therapies.

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