



Application of silver nanoparticles in food packages: a review

Emelda Orlando SIMBINE^{1,2}, Larissa da Cunha RODRIGUES², Judite LAPA-GUIMARÃES²,
Eliana Setsuko KAMIMURA², Carlos Humberto CORASSIN², Carlos Augusto Fernandes de OLIVEIRA^{2*} 

Abstract

Silver nanoparticles (AgNPs) are antimicrobial agents that have a wide spectrum of action, including against pathogenic bacteria and spoilage fungi. However, their mechanism of action is not completely clarified. Nowadays, scientific interest on biological synthesis of AgNPs is growing, with emphasis in their extracellular biosynthesis by microbial cells, as it is the most reliable and ecologically correct method for production, yielding no toxic residues. AgNPs may be incorporated to biodegradable and non-biodegradable polymers for the production of food packages with antimicrobial properties, leading to greater safety and longer shelf life. However, it is important to carry out migration tests for new food packages incorporated with AgNPs, based on the effective levels for their inclusion in the packaging materials.

Keywords: silver nanoparticles; antimicrobial activity; food packaging; polymers.

Practical Application: One of the main objectives of the food industry is to increase the shelf life of foodstuffs by using appropriate methods of microbial control in processes and products. In this context, results listed in the present review on the application of silver nanoparticles (AgNPs) in food packages offer new perspectives to prevent microbial spoilage and increase shelf life. However, AgNPs should be produced by ecologically correct methods, and the results from different studies regarding their antimicrobial effects should be critically evaluated before using these materials in food packages.

1 Introduction

Microbial contamination of foods is one of the main problems of the food industry, considering the waste of spoiled products and the implications to public health due to foodborne diseases (Carbone et al., 2016). Therefore, food quality assurance systems applied to production processes are essential to generate products that are free of microbiological hazards. Additionally, post-processing technologies may contribute for the maintenance of food quality during shelf life. Antimicrobial effects may be reached by direct incorporation of biocidal agents in foods or in the space around them (Carbone et al., 2016). In this context, active packages with antimicrobial properties have been developed for different foods, especially packages with active biocidal substances, which may increase the quality of the product, its shelf life, and prevent spoilage caused by microbial action (Fernández et al., 2010; Gallochio et al., 2016; Mahdi et al., 2012).

The first and most used materials in active packages were organic acids, enzymes, and polymers (biodegradable and non-degradable). Recently, nanoparticles (NPs) of metals or metallic oxides have been introduced with greater advantages compared with organic and inorganic acids, as they are resistant to the most severe processing conditions (Carbone et al., 2016), such as exposure to high temperatures (Emamifar et al., 2012). Nanotechnology is a promising interdisciplinary science in which new materials are developed in nanoscale, with applications in the fields of medicine, electricity, mechanics, catalysis, photonics, molecular computing, among others (Chen et al., 2016; Kanmani

& Lim, 2013). The introduction of nanotechnology in the food packaging industry may offer potential solutions for the challenge presented by short shelf life products, improving their quality and keeping them free of microbial adhesion (Emamifar et al., 2012; Qian et al., 2013). Metallic nanoparticles based on magnesium oxide, copper oxide, zinc oxide, cadmium selenite/tellurite, and titanium, silver and gold dioxide, have been studied because of their antimicrobial activity (AbdelRahim et al., 2017; Almeida et al., 2015; Echegoyen & Nerín, 2013; Silvestre et al., 2011).

Metallic NPs may be obtained by physical, chemical or biological methods, and antimicrobial activity varies according with the method of synthesis (Durán et al., 2010). Nowadays, research on biological synthesis of NPs has increased markedly, with emphasis in the microbial production of these compounds, as it is considered the most reliable and ecologically correct method (Wei et al., 2012). Among metallic nanoparticles, silver nanoparticles (AgNPs) have been widely studied due to their peculiar properties and their extensive application in the production of biomaterials (AbdelRahim et al., 2017), and in the food, cosmetics, clothing, and pharmaceutical industries (Chen et al., 2016; Kanmani & Lim, 2013). Additionally, when compared with other metals, silver presents the lowest toxicity for animal cells (Berni et al., 2008). Therefore, the most recent studies on antimicrobial nanocompounds in food packages are based on AgNPs (Emamifar et al., 2012; Gallochio et al., 2016; Martinez-Abad et al., 2012). Although AgNPs are listed by the

Received 14 Nov., 2018

Accepted 29 Mar., 2019

¹ Departamento de Para-Clínicas: Secção de Higiene e Tecnologia de Alimentos, Faculdade de Veterinária, Universidade Eduardo Mondlane, Maputo, Moçambique

² Departamento de Engenharia de Alimentos, Faculdade de Zootecnia e Engenharia de Alimentos, Universidade de São Paulo – USP, Pirassununga, SP, Brasil

*Corresponding author: carlosaf@usp.br

U.S. Food and Drug Administration as generally recognized as safe (GRAS) materials (Emamifar et al., 2012), there is a concern about the potential health effects associated with high intake levels caused by migration of these particles from the packaging to the foods (Claro & Magalhães, 2017; Echegoyen & Nerín, 2013; Gallochio et al., 2016). Thus, the objective of this paper is to review the available data published in the past 5 years on the mechanisms of action, microbial synthesis, toxicological aspects and antimicrobial properties of AgNPs, as well as their potential applications in the food industry.

2 Mechanisms of action of silver nanoparticles

According to Kanmani & Lim (2013), AgNPs have a wide spectrum of antimicrobial activity, including Gram-positive and negative bacteria, fungi, and viruses. It is known that AgNPs are toxic to a large variety of microorganisms (Morones et al., 2005) including *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus aureus*, *S. epidermidis*, *Vibrio cholerae*, *Pseudomonas aeruginosa*, *Shigella flexneri*, *Bacillus anthracis*, *B. subtilis*, *B. cereus*, *Proteus mirabilis*, *Salmonella enterica typhimurium*, *Micrococcus luteus*, *Listeria monocytogenes*, and *Klebsiella pneumoniae* (Almeida et al., 2015). The bactericidal effect of AgNPs was first quantified by Von Naegelis, using silver ions against algae (Berni et al., 2008). However, it is not clear if AgNPs present a specific mechanism of action (Morones et al., 2005), or if their antimicrobial activity is only associated with the release of Ag⁺ ions, their bioactive form (Almeida et al., 2015; Sobyte et al., 2015). On the other hand, Sobyte et al. (2015) proposed different mechanisms by which AgNPs inhibit or reduce the growth and metabolism of bacterial cells, leading to accelerated lysis.

The antimicrobial effect of silver, silver ions, and silver nanoparticles has been studied, aiming to evaluate the mechanism of action against a wide range of bacteria (Pal et al., 2007). Morones et al. (2005) evaluated the bactericidal effect of AgNPs, and identified three main mechanisms of action of the nanoparticles: (1) AgNPs in the range of 1 to 10 nm bound to the surface of the cell membrane and drastically interfere with its functions, such as permeability and respiration; (2) AgNPs are able to penetrate the bacterial cells and damage them, possibly by interacting with compounds containing sulfur and phosphorus, such as DNA; (3) AgNPs release silver ions, which are potentially very reactive and may react with the negatively charged cell membrane, providing an additional contribution to the bactericidal effect of silver nanoparticles.

A study carried out by Sobyte et al. (2015) demonstrated that, under anaerobiosis conditions, AgNPs do not show bactericidal effect, even at high concentrations. The authors supported the hypothesis that silver ions are not released in the absence of oxygen. Pal et al. (2007) observed different inhibition effects of AgNPs on *E. coli*, which activities varied according to the size and shape of particles. However, little is known about the change in AgNPs biological activity caused by the shape of the particle. According to Sobyte et al. (2015), AgNPs may have different shapes, but the most interesting particles in terms of antimicrobial effect are spherical and triangular, with greater antimicrobial effect of triangular particles than spherical possibly because of their larger contact surface.

3 Biosynthesis of silver nanoparticles and antimicrobial activity

The biological synthesis of AgNPs (involving bacteria, fungi, and biomolecules) has been widely researched, since it is considered as a reliable and ecologically correct method (Durán et al., 2010; Wei et al., 2012). Additionally, biological synthesis does not yield any toxic residues (Husseiny et al., 2015). Durán et al. (2010) reported that plant extracts may also be used in metallic nanoparticle production. Microbial synthesis of metallic NPs may be intracellular (Das et al., 2014) or extracellular (AbdelRahim et al., 2017; Das et al., 2014; Gopinath & Velusamy, 2013; Prakasham et al., 2014), yielding NPs of different sizes, shapes and antimicrobial efficacy (Husseiny et al., 2015).

Several studies have focused on extracellular synthesis of metallic nanoparticles because of its relative simplicity and lower cost compared with intracellular synthesis (Das et al., 2014). The mechanisms involved in the extracellular synthesis of nanoparticles using microorganisms have not been completely clarified. However, Das et al. (2014) postulated that the synthesis is related to the presence of nitrate reductase enzymes released by the microorganisms, which are responsible for the bio-reduction of metallic ions and metallic nanoparticles. This phenomenon may be evidenced by the color change using spectrophotometry (Elbeshehy et al., 2015). Taking into account the accessibility and easy genetic modification, bacteria are the most promising candidates to AgNPs synthesis (Wei et al., 2012; Elbeshehy et al., 2015; Kanmani & Lim, 2013; Singh et al., 2013b).

3.1 Biosynthesis of AgNPs by bacterial species

The main genera of bacteria that exhibit effective synthesis of AgNPs include *Bacillus* spp. (Das et al., 2014; Elbeshehy et al., 2015; Gopinath & Velusamy, 2013; Wei et al., 2012), *Streptomyces* spp. (Manikprabhu & Lingappa, 2013; Mohanta & Behera, 2014; Prakasham et al., 2014) *Acinetobacter* spp. (Singh et al., 2013b), and *Pseudomonas* spp. (Gopinath et al., 2017; Peiris et al., 2017). Bacterial strains used for AgNPs synthesis were mainly isolated in samples of soil sediment contaminated by heavy metals (Das et al., 2014; Elbeshehy et al., 2015; Mohanta & Behera, 2014), and marine sediments (Manivasagan et al., 2013; Prakasham et al., 2014). Table 1 presents the outcomes from recent studies on the bacterial biosynthesis of AgNPs, size and shape of AgNPs produced, as well as the microbial species tested for their minimum inhibitory concentration.

Kanmani & Lim (2013) synthesized bacterial AgNPs by direct reduction of silver nitrite by the exopolysaccharide, and demonstrated their antibacterial and antifungal activity with different susceptibilities of bacterial species in the following order: *P. aeruginosa* > *E. coli* and *K. pneumoniae* > *L. monocytogenes*. The inhibition zone observed for bacterial species was achieved at 2 mg/mL AgNPs, while fungal zone of inhibition ranged between 0.2 to 2 mg/mL, with greater susceptibility of *Aspergillus* spp. than *Penicillium* spp. AgNPs derived from *Acinetobacter* spp. biosynthesis using an extract of free cells of the microorganism had antimicrobial activity against Gram-positive and negative bacteria (Singh et al., 2013b). Wei et al. (2012) produced bacterial

Table 1. Antimicrobial effect of silver nanoparticles synthesized by bacterial strains.

Producer species	Particle size (nm)	Particle shape	Microbial species tested	MIC (mg/mL)	Reference
<i>Acinetobacter calcoaceticus</i> LRVP54	8-12	NI	<i>P. aeruginosa</i> and <i>A. Baumannii</i> <i>S. aureus</i> and <i>S. mutans</i>	150-600 >1.000	Singh et al. (2013a)
Acid lactic bacteria	2-15	Spherical Triangular	<i>P. aeruginosa</i> , <i>E. coli</i> , <i>Klebsiela pneumonia</i> and <i>L. monocytogenes</i> <i>Aspergillus</i> spp. and <i>Penicillium</i> spp	2 0.2-2	Kanmani & Lim (2013)
<i>Bacillus</i> spp. GP-23	7-21	Spherical	<i>F. oxysporum</i>	0.08	Gopinath & Velusamy (2013)
<i>Stenotrophomonas maltophilia</i> (GenBank: JN247637.1)	93	Cubic	<i>S. aureus</i> , <i>E. coli</i> and <i>S. marcescens</i>	0.0125-0.05	Oves et al. (2013)
<i>Nocardiopsis</i> spp. MBRC-1	30-90	Spherical	<i>B. subtilis</i> ATCC 6633 <i>P. aeruginosa</i> ATCC 27853 and <i>C. albicans</i> ATCC 10231 <i>E. coli</i> ATCC 10536 13 and <i>A. fumigatus</i> ATCC 1022 <i>S. aureus</i> ATCC 6538 <i>E. hirae</i> ATCC 10541 and <i>A. niger</i> ATCC 1015 <i>S. flexneri</i> ATCC 12022 and <i>A. brasiliensis</i> ATCC 16404	0.007 0.01 0.013 0.014 0.016 0.018	Manivasagan et al. (2013)
<i>Streptomyces coelicolor</i>	28-50	Irregular	methicillin-resistant <i>S. aureus</i>	0.03	Manikprabhu & Lingappa (2013)
<i>Streptomyces parvulus</i> SSNP11	1.7-11.7	Spherical	<i>P. putida</i> , <i>S. typhi</i> , <i>B. subtilis</i> and <i>K. pneumoniae</i>	NI	Prakasham et al. (2014)
<i>Streptomyces</i> spp. SS2	67.9 ± 18.5	Spherical	<i>E. coli</i> (MTCC 1089), <i>B. subtilis</i> (MTCC 7164), <i>S. epidermitis</i> (MTCC 3615), <i>V. cholerae</i> (MTCC 3904), and <i>S. aureus</i> (MTCC 1144)	NI	Mohanta & Behera (2014)
<i>Bacillus licheniformis</i> (NPs-3)	77-92	Triangular, hexagonal and spherical	<i>E. coli</i> , <i>S. sonnei</i> and <i>K. pneumonia</i> <i>P. aeruginosa</i> <i>S. aureus</i> <i>S. bovis</i>	0.0032 0.0063 0.0125 0.025	Elbeshehy et al. (2015)
<i>Pseudomonas aeruginosa</i> ATCC 27853	33-300	Spherical	<i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>S. typhimurium</i> , <i>Acinetobacter</i> and <i>C. albicans</i>	NI	Peiris et al. (2017)
<i>Streptococcus</i> spp. <i>durhamensis</i>	100-700	Spherical	<i>S. aureus</i> ATCC6338, <i>B. subtilis</i> PCM2021, <i>E. coli</i> ATCC8739, <i>K. pneumoniae</i> ATCC700603 and <i>S. infantis</i> <i>P. mirabilis</i> <i>P. aeruginosa</i> ATCC10145	0.00625 0.05 0.025	Buszewski et al. (2018)
<i>Bacillus</i> spp. SBT8	1-20	Spherical and pseudo-spherical	<i>L. monocytogenes</i> <i>S. aureus</i> <i>E. coli</i> O157:H7 <i>S. typhimurium</i> <i>P. aeruginosa</i>	0.4 0.1 0.6 0.4 0.6	Yurtluk et al. (2018)
<i>Pseudomonas</i> spp. THG-LS1.4	10-40	Irregular	<i>B. cereus</i> , <i>S. aureus</i> , <i>C. tropicalis</i> , <i>V. parahaemolyticus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> and <i>S. enterica</i>	NI	Singh et al. (2018)
<i>Streptomyces xinghaiensis</i> OF1	5-20	Spherical and polydispersed	<i>P. aeruginosa</i> ATCC 10145 <i>E. coli</i> ATCC 8739 <i>B. subtilis</i> PCM 2021 <i>K. pneumoniae</i> ATCC 700603 <i>S. aureus</i> ATCC 6538 <i>C. albicans</i> ATCC 10231 <i>M. furfur</i> DSM 6170	0.016 0.064 0.256 0.032 0.032 0.032 0.032	Wypij et al. (2018)
<i>B. brevis</i> (NCIM 2533)	22-60	Spherical	<i>S. aureus</i> and <i>S. typhi</i> using	NI	Saravanan et al. (2018)
<i>E. coli</i>	33.6	Spherical	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i> and <i>S. aureus</i>	NI	Neihaya & Zaman (2018)
<i>Pseudomonas aeruginosa</i> ATCC 27853	33-300	Spherical	<i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>S. typhimurium</i> , <i>Acinetobacter</i> and <i>C. albicans</i>	NI	Peiris et al. (2017)
<i>Bacillus licheniformis</i> (NPs-3)	77-92	Triangular, hexagonal and spherical	<i>E. coli</i> , <i>S. sonnei</i> and <i>K. pneumonia</i> <i>P. aeruginosa</i> <i>S. aureus</i> <i>S. bovis</i>	0.0032 0.0063 0.0125 0.025	Elbeshehy et al. (2015)

MIC: Minimum inhibitory concentration; NI: Not informed.

AgNPs from *Bacillus amyloliquefaciens* by solar irradiation, and these nanoparticles presented antimicrobial effects, with *B. subtilis* being more susceptible (0.009 mg/mL) than *E. coli*. Gopinath & Velusamy (2013) synthesized AgNPs using *Bacillus* spp. GP-23, and observed effective antifungal activity against *Fusarium oxysporum* at 0.008 mg/mL.

Bacillus spp. strains isolated from soil samples contaminated with heavy metals were highly efficient for intracellular and extracellular synthesis of AgNPs (spherical, 42-92 nm) (Das et al., 2014). Elbeshehy et al. (2015) identified new strains of *Bacillus* (*B. pumilus*, *B. persicus*, and *B. licheniformis*) that were efficient in the AgNPs extracellular synthesis. AgNPs produced by *B. licheniformis* presented strong antibacterial effect against Gram-negative bacteria (*E. coli*, *K. pneumoniae*, *S. sonnei*, *P. aeruginosa*), followed by Gram-positive ones (*S. epidermidis*, *S. aureus* - methicillin-resistant strain - and *S. bovis*). Significant antifungal effects were also observed against *A. flavus* and *C. albicans* ATCC 1021.

AgNPs produced by *Streptomyces albidoflavus* were evaluated by Prakasham et al. (2012) by determining the inhibition zones against bacterial species. The author observed high antibacterial effects against *K. pneumoniae* (36 mm), followed by *M. luteus* (28 mm), and *B. subtilis* (24 mm), and lower effect against *E. coli* (22 mm). On the other hand, Mohanta & Behera (2014) developed the extracellular biosynthesis of AgNPs using *Streptomyces* sp. SS2 isolated from soil sediment samples, and demonstrated potential antimicrobial activity of AgNPs against *E. coli*, *B. subtilis*, *S. epidermidis*, *V. cholerae*, and *S. aureus*. The largest and the smallest zone of inhibition were observed against *V. cholerae* and *B. subtilis*, respectively.

Prakasham et al. (2014) characterized AgNPs obtained from extracellular synthesis by strains of actinomycetes (*Streptomyces parvulus* SSNP11) isolated from samples of marine sediment. The AgNPs had effective antibacterial activity against Gram-negative and positive bacteria, including *P. putida*, *K. pneumoniae*, *B. subtilis*, and *S. typhi*. Manivasagan et al. (2013) studied the biosynthesis of AgNPs (spherical, average size 45 ± 0.15 nm) by *Nocardiopsis* sp. MBRC-1 isolated from samples of marine sediment. The resulting particles had significant antimicrobial effects against several microorganisms including bacteria (*E. coli*, *B. subtilis*, *E. hirae*, *P. aeruginosa*, *S. flexneri*, and *S. aureus*) and fungi (*A. niger*, *A. brasiliensis*, *A. fumigates*, and *C. albicans*).

Peiris et al. (2017) produced AgNPs using *Pseudomonas aeruginosa* ATCC 27853, and demonstrated that the nanoparticles were effective against Gram-negative and positive bacteria (*E. coli* ATCC 25922, *S. aureus* ATCC 25923, *P. aeruginosa* ATCC 27853, *S. typhimurium*, *Acinetobacter*) as well as fungi (*C. albicans*). Gopinath et al. (2017) obtained AgNPs by biogenic extracellular synthesis using the bacterium *P. putida* MVP2. The AgNPs were efficient against Gram-positive and negative bacteria, including *S. aureus*, *E. coli*, *B. cereus*, *P. aeruginosa*, and *H. pylori*. AgNPs produced by biosynthesis using the acidophilic actinobacterium *Streptacidiphilus durhamensis* HGG16n had high antimicrobial effect against *P. aeruginosa*, *S. aureus*, and *P. mirabilis*, followed by *E. coli*, *K. pneumoniae*, and *B. subtilis* (Buszewski et al., 2018).

In summary, low levels of AgNPs synthesized by bacterial species presented strong antimicrobial activity effect against *S. aureus*, *P. aeruginosa*, *B. subtilis*, *E. coli*, although higher concentrations were required to become effective against other important pathogenic microorganisms including *L. monocytogenes* and *S. typhimurium*.

3.2 Biosynthesis of AgNPs by fungi species

There are several reports demonstrating the biosynthesis of AgNPs by fungi species, mostly of them related to the use of endophytic fungi (those isolated from parts of plants) (Devi & Joshi, 2015; Qian et al., 2013; Singh et al., 2017; Sogra Fathima & Balakrishnan, 2014). The main genera of fungi reported as efficient in extracellular biosynthesis of AgNPs include *Fusarium* spp. (Balakumaran et al., 2015; Husseiny et al., 2015; Sogra Fathima & Balakrishnan, 2014), *Aspergillus* (Balakumaran et al., 2015; Devi & Joshi, 2015; Ninganagouda et al., 2013), and *Penicillium* (Balakumaran et al., 2015; Devi & Joshi, 2015; Ma et al., 2017; Singh et al., 2013a). AgNPs produced by fungal biosynthesis have antimicrobial properties against a wide range of pathogenic microorganisms, including fungi, Gram-positive and negative bacteria, as shown in Table 2.

Gade et al. (2013) studied the ability of 18 species in the genus *Phoma* spp. to produce AgNPs, and concluded that all of them were efficient in terms of AgNPs biosynthesis. In general, the process yielded spherical nanoparticles, except for the species *P. sorghina* MTCC-2096, which produced AgNPs in the shape of nanorods. Sogra Fathima & Balakrishnan (2014) studied the extracellular biosynthesis and optimization of AgNPs, using the endophytic fungus *Fusarium solani*. These authors obtained AgNPs of different shapes, with the predominance of 10-nm, spherical AgNPs. Husseiny et al. (2015) demonstrated that the AgNPs (spherical and uniformly distributed) synthesized by *Fusarium oxysporum* were effective against *S. aureus* and *E. coli*. Ninganagouda et al. (2013) reported AgNPs extracellular biosynthesis by *Aspergillus flavus*, which were efficient against the Gram-negative bacteria tested, *P. aeruginosa*, *E. coli* and *K. pneumoniae*.

Regarding the antifungal properties of AgNPs from fungal biosynthesis, Qian et al. (2013) observed a high extracellular biosynthesis of AgNPs by the endophytic fungus *Epicoccum nigrum* isolated from *Phellodendron amurense*. The antifungal activities of the AgNPs obtained were demonstrated against 9 fungus strains (*Candida albicans* ATCC 90028, *C. parapsilosis* ATCC 22019, *C. tropicalis* JLCC 31384, *C. krusei* ATCC 6258, *Cryptococcus neoformans* IFM 45687, *A. fumigatus* IFM 40808, *A. flavus* IFM 55648, *F. Solani* JLCC 30866, and *Sporothrix schenckii* JLCC 32757). Studies demonstrated that endophytic fungi (*Aspergillus tamarii* PFL2, *Aspergillus niger* PFR6 and *Penicillium ochrochloron* PFR8) isolated from the ethno medicinal plant *Potentilla fulgens* L. also show the ability to synthesize AgNPs (Devi & Joshi, 2014, 2015). *Cryptosporiopsis ericae* PS4 was also efficient for extracellular biosynthesis of AgNPs, which were effective against pathogenic microorganisms, including *S. aureus* MTCC96, *S. enteric* MTCC735, *E. coli* MTCC730, *E. faecalis* MTCC2729, and *C. albicans* MTCC 183 (Devi & Joshi, 2014). Chen et al. (2016) produced AgNPs using an exopolysaccharide obtained

Table 2. Antimicrobial effect of silver nanoparticles synthesized by fungus strains.

Producer species	Particle size (nm)	Particle shape	Microbial species tested	MIC (mg/mL)	Reference
<i>Aspergillus flavus</i>	NI	NI	<i>P. aeruginosa</i> , <i>E. coli</i> and <i>K. pneumoniae</i>	0.02	Ninganagouda et al. (2013)
<i>Epicoccum nigrum</i>	1-22	Spherical	<i>C. tropicalis</i> , <i>F. solani</i> and <i>A. fumigatus</i>	0.001	Qian et al. (2013)
			<i>C. neoformans</i> and <i>S. schenckii</i>	0.00025	
			<i>A. flavus</i> and <i>C. albicans</i>	0.0005	
			<i>C. parapsilosis</i> and <i>C. krusei</i>	0.0000125	
<i>Cryptosporiopsis ericae</i> PS4	2-15	Spherical	<i>E. coli</i> MTCC730 and <i>S. enterica</i> MTCC735	0.0015	Devi & Joshi (2014)
			<i>S. aureus</i> MTCC96 and <i>E. faecalis</i> MTCC2729	0.002	
			<i>C. albicans</i> MTCC183	0.0001	
<i>Aspergillus tamarii</i>	3.5 ± 3.3	Spherical	NI	NI	Devi & Joshi (2015)
<i>Aspergillus niger</i>	8.7 ± 6				
<i>Penicillium ochrochloron</i>	7.7 ± 4.3				
<i>Fusarium oxysporum</i>	5-13	Spherical	<i>E. coli</i> and <i>S. aureus</i>	0.08	Husseiny et al. (2015)
<i>Guignardia</i> spp.	5-30	Spherical	<i>P. mirabilis</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> and <i>S. aureus</i>	0.003	Balakumaran et al. (2015)
			<i>E. coli</i> , <i>S. epidermidis</i> and <i>B. subtilis</i>	0.00625	
			<i>E. faecalis</i>	0.000125	
Cs-HK1 fungus (not specified)	30-40	-	<i>E. coli</i>	1.6	Chen et al. (2016)
<i>Penicillium aculeatum</i> Su1	4-55	Spherical	<i>E. coli</i> ATCC-8739, <i>P. aeruginosa</i> , ATCC-15442, <i>S. aureus</i> ATCC, <i>B. subtilis</i> , ATCC-663, <i>C. albicans</i> ATCC-10231	0.05-0.2	Ma et al. (2017)
<i>Alternaria</i> spp.	10-30	Spherical	methicillin-resistant <i>B. subtilis</i> , <i>S. aureus</i> , <i>E. coli</i> and <i>S. marcescens</i>	NI	Singh et al. (2017)
<i>Fusarium oxysporum</i>	34-44	NI	<i>E. coli</i>	11.1	Hamedi et al. (2017)
<i>Ganoderma enigmaticum</i> and <i>Trametes ljubarskyi</i>	15	Spherical	<i>B. subtilis</i> MTCC 441, <i>S. aureus</i> MTCC 96, <i>M. luteus</i> KUCCC 4, <i>Staphylococcus</i> KUCC 7, <i>E. coli</i> MTCC 443, <i>P. putida</i> KUCCC 12, <i>K. pneumoniae</i> MTCC 109 and <i>K. aerogenes</i> MTCC 98	NI	Gudikandula et al. (2017)
<i>Penicillium polonicum</i>	10-15 > 30	Spherical and nonspherical polyhedral	<i>Acinetobacter baumani</i> ,	0.156	Neethu et al. (2018)
<i>Fusarium semitectum</i> and <i>Aspergillus niger</i>	10-25	Spherical	<i>E. coli</i> (ATCC-8739), <i>S. aureus</i> (ATCC-6538) and <i>P. aeruginosa</i> (ATCC-15442)	NI	Madakka, Jayaraju, & Rajesh (2018)
<i>Phenerochaete chrysosporium</i> (MTCC- 787)	34-90	Spherical and oval	<i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>S. aureus</i> and <i>S. epidermidis</i>	NI	Saravanan et al. (2018)
<i>Fusarium oxysporum</i>	1-50	Spherical	<i>E. coli</i> and <i>P. aeruginosa</i>	0.01	Srivastava et al. (2019)

MIC: Minimum inhibitory concentration; NI: Not informed.

by means of fermentation of a medicinal fungus and AgNO₃ in distilled water. These nanoparticles showed antimicrobial effect against Gram-positive and negative bacteria.

The aqueous extract of the mycelium of *Rhizopus stolonifer* demonstrated to be effective in the biosynthesis of spherical AgNPs (diameter: 9.46 ± 2.64 nm) (AbdelRahim et al., 2017). The AgNPs produced by the fungus *Cordyceps sinensis* (Berk.) Sacc Cs-HK1, presented antimicrobial activity against *E. coli* (1.6 mg/mL) and *S. aureus* (0.8 mg/mL) (Chen et al., 2016). Singh et al. (2017) reported the extracellular biosynthesis of spherical AgNPs (diameter: 4-30 nm) using the supernatant of an endophytic fungus (*Alternaria* spp) isolated from *Raphanus sativus*, which showed antimicrobial properties against pathogenic bacteria (methicillin-resistant *B. subtilis*, *S. aureus*, *E. coli* and

S. marcescens). The endophytic fungus *Penicillium* spp. isolated from the leaves of *Curcuma longa* was efficient in the extracellular biosynthesis of spherical AgNPs (diameter: 25 nm), which was effective against several pathogens, especially *P. aeruginosa* and *K. pneumoniae* (Singh et al., 2013a).

Balakumaran et al. (2015) isolated 13 species of endophytic fungi in 9 different samples of plant leaves, and observed that only 6 fungi (*A. niger*, *Aspergillus* spp., *Colletotrichum* spp., *F. oxysporum*, *Guignardia* spp., and *Penicillium* spp.) were able to produce AgNPs by extracellular biosynthesis. In particular, *Guignardia* spp., isolated from *Citrus* spp., showed the best results for extracellular biosynthesis of AgNPs that were effective against several Gram-negative and Gram-positive bacterial species, including *E. coli* ATCC 8739, *Proteus mirabilis* MTCC 425,

P. aeruginosa ATCC 27853, *S. aureus* ATCC 29736, *E. faecalis* ATCC 29212 and *B. subtilis* ATCC 6633. AgNPs produced by the fungus *Penicillium aculeatum* Su1 also presented antimicrobial activity against Gram-negative and positive bacteria and fungi at levels of 0.05-0.2 mg/mL, with greatest effect on *C. albicans*, followed by *P. aeruginosa*, *B. subtilis*, *S. aureus* and *E. coli* (Ma et al., 2017).

4 Application of silver nanoparticles in food packaging

Many of the packages used in the food industry are made of petroleum-based plastics. When compared with other materials (paper, glass, wood, metals and ceramic), plastic packages have advantages in terms of physical-mechanic characteristics, such as weight, flexibility, mechanical resistance, and physical-chemical and biological characteristics related to quality, health protection and safety (Claro & Magalhães, 2017). These features provide to plastic materials excellent conditions to produce active packages obtained by the addition of nanocompounds with antimicrobial properties. According to Almeida et al. (2015), packages with nanotechnological applications have better

physical-chemical properties, reduced hydrophilic characteristics, better biodegradability, and increased value-added. Active packages make up a new generation of food packages obtained by the incorporation of metallic nanoparticles to polymer films (Emamifar et al., 2012).

The advantage of silver antimicrobial agents is that they can be easily incorporated to several materials, such as plastics and textiles, making them useful in wide spectrum applications, maintaining their antimicrobial activity *in situ*, in which traditional antimicrobial agents would be unstable (Almeida et al., 2015). According to Carbone et al. (2016), AgNPs may be incorporated to non-degradable (polyethylene, polyvinyl chloride, vinyl alcohol) and biodegradable polymers (cellulose, starch, chitosan, agarose) to produce food packages, as presented in Table 3.

Emamifar et al. (2012) evaluated the inhibition effect of packages impregnated with Ag and ZnO nanoparticles on *Lactobacillus plantarum* in orange juice, and observed that the bacterium was inhibited in the product stored at 4 °C. However, the silver nanoparticle presented the greatest antimicrobial activity, compared with the ZnO nanoparticle, in juices stored for up to 112 days. Panea et al. (2014) demonstrated the antimicrobial

Table 3. Antimicrobial effect of silver nanoparticles (AgNP) incorporated to food packages.

AgNP characteristics	Package	Food product	Storage conditions	Antimicrobial effect	Reference
Spherical (40-50 nm)	PVC	Minced beef	3 ± 1 °C for 14 days	Inhibitory effect on microbial growth after 7 days for mesophilic, total bacteria and <i>S. aureus</i> , and after 10 days for <i>E. coli</i>	Mahdi et al. (2012)
Zinc oxide + AgNP	LDPE	Chicken breast cooked	4 °C for 21 days	Inhibitory effect on Enterobacteriaceae and mesophilic bacteria	Panea et al. (2014)
Pullulan + spherical (40-100 nm)	NI	Raw turkey breast, raw beef, and ready-to-eat turkey breast	4 °C for 21 days	Effectiveness against <i>S. aureus</i> , <i>L. monocytogenes</i> , <i>E. coli</i> O157:H7	Morsy et al. (2014)
Spherical (3-20 nm)	LDPE	Fresh pork sirloin	6 °C for 28 days	Decrease in viable counts of <i>L. piscium</i> , <i>B. thermosphacta</i> , <i>H. alvei</i> , <i>L. sakei</i> and <i>C. divergens</i>	Kuuliala et al. (2015)
Spherical (10.10 + 0.60 nm)	LDPE	Chicken breast fillet	4 °C for 12 days	Changes in viable counts of psychrotrophic bacteria, <i>Pseudomonas</i> spp., lactic acid bacteria, <i>B. thermosphacta</i> , <i>E. coli</i> , and total coliforms	Azlin-Hasim et al. (2015)
NI	Plastic	Fresh chicken meatballs	5 ± 1 °C for 7 days	Effectiveness against Enterobacteriaceae and <i>Pseudomonas</i> spp.	Gallocchio et al (2016)
Spherical (35 nm) + CuO (50 nm) + ZnO (50-30 nm) AgNPs	LDPE	Ultra-filtrated cheese	4 ± 0.5 °C for 28 days	Decrease in the most probable number of coliforms	Beigmohammadi et al. (2016)
AgNPs	PVC	Walnut, hazelnut, pistachio almond	Room temperature, 24 months	Decrease total bacteria count and coliform	Tavakoli et al. (2017)
TiO ₂ +Ag (10nm)	PLA	Yunnan cottage cheese	5 ± 1 °C for 25 days	Inhibitory effect against total bacteria count, yeasts and molds growth	Li et al. (2018)
Bergamot essential oils + TiO ₂ + AgNPS	PLA	Mangoes	Room temperature, 15 days	Effectiveness against total bacteria count	Chi et al. (2019)

PVC: Polyvinyl chloride; LDPE: Low density polyethylene; PLA: Poly lactic acid matrix; NI: Not informed.

effect of nanocomposite packages of chicken breast containing different ZnO and Ag ratios. However, the authors observed that the meat sensory attributes were slightly affected by the package, with increased cereal odor and tenderness after 10 days of storage, although no differences were found in color and appearance of the product after 21 days of storage.

Fernández et al. (2010) stored fresh melon cuts in plastic films based on cellulose incorporated with spherical AgNP (5 and 35 nm diameters), and obtained low counts of yeasts, mesophilic and psychrophilic bacteria, when compared with the control films (without AgNP). Beigmohammadi et al. (2016) developed low density polyethylene (LDPE) package films incorporated with Ag, copper oxide (CuO), and zinc oxide (ZnO), and found a reduction in coliform counts of ultra-filtered cheese stored at 4 ± 0.5 °C for 4 weeks.

Azlin-Hasim et al. (2015) studied the effect of the combination between LDPE film package with AgNPs and modified atmosphere in the shelf life of chicken breast fillets. Two films were developed with the incorporation of AgNPs in the polymer (0.5 and 1% polymer weight, w/w), and tested for their antimicrobial activity against several bacterial species. Compared with the control film (without AgNPs), bacterial growth in the nanocomposite Ag/LDPE film was significantly inhibited until day 6 (up to 22.5% reduction), which significantly increased the shelf life of the chicken breast fillet. Kuuliala et al. (2015) also developed LDPE package films containing AgNPs to protect fresh pork sirloin stored at 6 °C for 28 days. The antimicrobial effect of the films against the bacteria associated with meat spoilage was determined, including *Leuconostoc gelidum* subsp. *gasicomitatum* (LMG 18811T), *Lactobacillus sakei* (23K), *Lactococcus piscium* (MKFS47), *Carnobacterium divergens* (DSMZ 20623T) and *Hafnia alvei* (DSMZ30163). In the *in vitro* study of the films, they were effective against *L. piscium*, *B. thermosphacta*, *H. alvei*, *L. sakei* and *C. divergens*. However, the AgNPs films did not affect the microbial growth in the packed samples of pork sirloin during storage, when compared with the control. This finding was attributed to the different dynamics in silver ion release on meat surfaces, or to the interaction between silver and amino acids.

5 Toxicological aspects of silver nanoparticles

In spite of all the advantages related to the use of AgNPs, one possible constraint in the use of nanoparticles in food packages is their migration to the food, leading to potential toxicity problems (Panea et al., 2014). Echegoyen & Nerin (2013) assessed Ag migration in three types of containers available in the USA, including polypropylene plastic bags and polyolefin containers. Ag migration was tested using two simulated food conditions using ethanol (50% v/v) and acetic acid (3% v/v) at 40 °C for 10 days and 70 °C for 2 h. The authors demonstrated the migration of Ag from the package to the liquid, which was greater in acetic acid at 40 °C for 10 days. However, total Ag migration was below the maximum migration limits determined by European regulations. Jokar & Abdul Rahman (2014) assessed the Ag⁺ migration in simulated food conditions (distilled water, 3% acetic acid, 10% ethanol) and in apple juice stored at 4 and 40 °C for 30 days. The migrated AG from package to the acetic acid solution and apple juice was higher than in ethanol

and distilled water, indicating that acidity promotes Ag⁺ release by the polymers due to their dissolution.

Recent studies have investigated the effects of AgNPs *in vivo* and *in vitro* (Garcia et al., 2016). AgNPs may accumulate in several organs, including the liver, kidneys, testicles, and brain (Bagheri-Abassi et al., 2015; Garcia et al., 2016). Garcia et al. (2016) demonstrated that the oral exposure of Sprague Dawley adult rats to subchronic doses of AgNPs led to an accumulation of Ag in different tissues at doses of 50, 100 and 200 mg/kg/day. Moreover, high doses of AgNPs can cause hepatotoxic (El Mahdy et al., 2015), neurotoxic (Bagheri-Abassi et al., 2015), and genotoxic effects (El Mahdy et al., 2015; Patlolla et al., 2015). However, the possibility of migration of such toxic levels from active packages to foods is very low, although possible toxicological effects of AgNPs levels in foods as a consequence of migration from packages have not been assessed so far.

Li et al. (2018) evaluated the migration of AgNPs of poly (lactic acid) (PLA) matrix impregnated with TiO₂ + AgNPs in Yunnan cottage cheese. The authors observed that the Ag ions migration (0.02 mg/kg) into the food increased with storage time. However, the total Ag migration was lower than the maximum migration limits (10 mg/Kg) determined by European regulations for food contact material. Chi et al. (2018) studied the migration behavior of AgNPs from the PLA films in the presence of 50% (v/v) ethanol as a food simulant. The author reported that high pressure treatment at 200 to 400 MPa reduced the migration of AgNPs from the films. The amounts of AgNPs migrated were 0.354 and 0.409 mg/Kkg for treatment at 200 to 400 MPa, respectively. Thus, the author conclude that the PLA films treated by high pressure were safe and suitable for contact with foodstuffs.

6 Conclusions

Silver nanoparticles are potential antimicrobial agents against a wide range of microorganisms, including highly pathogenic Gram-positive and Gram-negative bacteria and fungi. Biological synthesis of AgNPs is considered the most correct and reliable method to obtain these particles. The use of bacteria and fungi has been widely explored for extracellular biosynthesis of AgNPs, demonstrating to be efficient and promising. Polymers are the main materials tested for impregnation with AgNPs to produce active food packages. However, it is important to carry out migration tests when a new package based on AgNP is produced. Additionally, further studies are necessary to determine the effective levels for AgNP inclusion in food packages.

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