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Review Article

A Ride on The Current State of Silver Nanoparticles in Health: What is The Next Stop?

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Abstract
Silver nanoparticles (AgNPs) are known for their broad scientific and technological applications, among which those related to their bioactivity stand out the most. Its antimicrobial, antioxidant, anti-inflammatory, anti-obesity, antifouling, and biosorption properties have been widely studied and analyzed. Furthermore, numerous strategies are being investigated to overcome the main limitation of AgNPs, their cytotoxicity, such as the development of green chemistry synthesis methods using plant extracts or the use of support materials for controlled release of nanoparticles. However, the methodologies currently used in this line of research limit these nanomaterials from eventually being used in the clinic. It is necessary to implement animal models and interdisciplinary collaboration with biomedical research groups to develop therapies based on AgNPs that may be able to have an impact on the health of patients.

Keywords: silver nanoparticles, bioactivity, cytotoxicity, green synthesis, support material, animal model, interdisciplinary, biomedical research

1. INTRODUCTION

In the late 1950s, the study of materials on the scale of nanometers led to the emergence of nanoscience [1], which soon had practical applications through nanotechnology, such as nanosensors, nanocarriers, and nanomaterials [2][3]. These new materials present a practically infinite number of applications, which even today are the driving force of unimaginable technological advances across various industries, such as agrotechnology [4], food industry [5], construction industry [6], cosmetics [7], and catalytic chemistry industry [8]. The incredible versatility of these nanomaterials is due, among other aspects, to their small size (ranging from 1 to 100 nm) [9], which allows them to carry out their action at a microscopic level.

Among the amalgamation of nanomaterials that currently exist, silver nanoparticles (AgNPs) have become one of the most researched and used [10]. Some of the factors that contribute to their versatility and attractive applications are their versatile shapes or their easy-tunable properties, such as their unique physicochemical properties [11]-[14]. However, the most important factor may be their small size, which has allowed them to have a significant impact on technological advancements and applications across different industries because it allows them to interact with other substances and exert their action at the molecular level [15]. As a result, many scientific fields benefit from them: catalysis, textiles, environmental science, and food agriculture are just some examples [16]. Thus, this type of research is state-of-the-art, and recent literature reports the use of AgNPs with wondrous purposes such as air [17] and water filters [18], food packaging [19], in cotton fabrics [20], and as a catalyst in degradation reactions [21]. Finally, AgNPs are a great example of bio-nanoscience, a field that focuses on better understanding the interaction of nanomaterials with biological systems [22], which is why recent research is demonstrating the wide range of attractive bioactivities that AgNPs can present.

This review aims to focus on the applications that derive from this last characteristic of AgNPs, their bioactivity, both from present and future panoramas. In the first section, the bioactivities of AgNPs will be presented, both those that are well-known and those that have been recently discovered and are not fully understood. In the second section, their main drawback, toxicity, will be analyzed, as

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well as the strategies that are being developed to overcome it. Finally, considering the ultimate goal of this line of research is developing AgNPs as potent therapeutic agents against human diseases, the limitations of current research and future perspectives will be discussed.

2. SILVER NANOPARTICLES AS BIOACTIVE AGENTS

Among all its top-notch applications, the well-known bioactivity of AgNPs has made this nanomaterial fully enter biomedical research [23]. There are numerous studies carried out to exploit their antibacterial, antiviral, antifungal, antioxidant, anti-inflammatory, anti-obesity, antifouling, and biosorptive properties. Firstly, of all of them, the most studied is surely its antibacterial activity. Thus, AgNPs have been shown to have activity against many different bacteria, both Gram-negative such as *Escherichia coli* [24] and *Salmonella typhi* [25], and Gram-positive like *Staphylococcus aureus* [26] and *Bacillus cereus* [27]. In fact, given the growing challenge of antibiotic resistance, AgNPs have been proposed as a possible solution to the problem, and their effectiveness has already been demonstrated in multidrug-resistant strains of *Mycobacterium tuberculosis* [28], *Staphylococcus pseudintermedius* [29] or *Klebsiella pneumoniae* [30].

AgNPs also have antiviral properties, as their effectiveness has been seen against influenza A [31], herpes simplex type 1 [32] and SARS-CoV-2 [33] viruses, and antifungal, being effective against *Candida spp.* [34], *Fusarium spp.* [35], and *Aspergillus spp.* [36]. Its antioxidant potential is also widely documented, this capacity being normally demonstrated with 2,2-diphenyl-1-picrylhydrazyl (DPPH) [37] but also with other chemical species such as H_2O_2 [38] or Fe^{3+} [39]. Its anti-inflammatory activity has been demonstrated through the measurement of levels of IL-1β, IL-6, IL-18, and TNF-α through enzyme-linked immunosorbent assays (ELISA) both *in vitro* and *in vivo* experiments [14][40]. Something similar has happened with its anti-obesity capacity, which has been studied both *in vitro* [41] and in rats [42]. The antifouling and biosorptive properties of AgNPs have also been investigated, achieving, for example, the removal of nonsteroidal anti-inflammatory drugs (NSAID) from aqueous media [18][43]. Finally, recent studies go further and postulate that the bioactivity of AgNPs may not be limited solely to the above and propose antidiabetic [44], anticoagulant [45], thrombolytic [46], antinociceptive [47], and even anticholinesterase activities [48].

3. ON THE WAY TO OVERCOMING TOXICITY

Although AgNPs may be very attractive due to their bioactivity and their arsenal of applications, their use may be limited by their potential toxicity, which is the main problem of this nanomaterial [49]. AgNPs are known to be toxic to eukaryotic cells in a size-dependent manner: the smaller the AgNPs, the higher the cytotoxicity [50]. This effect is mediated by different mechanisms, such as the induction of higher levels of reactive oxygen species (ROS) [51] or lactate dehydrogenase (LDH) [52]. Furthermore, these cellular changes can produce cell necrosis and cause tissue damage [53]. These attacks on the biocompatibility of AgNPs hinder the applicability of this nanomaterial in biological systems and limit its safe medical applications, which will be discussed in more depth in the following section.

Consequently, and due to these risks that they may pose to human health [54], numerous studies are currently focusing on investigating the toxicity of AgNPs and possible strategies to overcome it. Firstly, there are various methods for the synthesis of AgNPs, the best known being chemical reduction. This consists of starting from a silver precursor such as $AgNO_3$ and reducing it to elemental silver using chemical-reducing agents [55]. However, many of these chemicals and solvents are toxic and determine the final toxicity of the AgNPs [56]. Faced with this, the development of green chemistry has made it possible to obtain green synthesized AgNPs using vegetable extracts as reducing agents [57], thus achieving a much more sustainable and toxic-free material [58]. This line of research is currently being widely exploited, and numerous studies can be found in the literature that use vegetable compounds as reducing agents, as shown in Table 1.

Table 1. Some of the papers published in 2024 reporting the use of vegetable extracts for the green synthesis of AgNPs and the study of their bioactivity.

Study	Vegetable extract employed	Bioactivity studied	Ref.
Alotaibi et al.	*Olea europaea* (olive)	Antifungal and antiparasitic	[59]
Araújo et al.	*Croton urucurana* (Dragon's blood)	Toxicity	[60]
Ghasemi et al.	*Rubus discolor* (Himalayan blackberry)	Antibacterial and anticancer	[61]
Karan et al.	*Sambucus ebulus* (danewort)	Antibacterial and antioxidant	[62]
Kaur et al.	*Lycium shawii* (Arabian boxthorn)	Antibacterial, antifungal, and antioxidant	[63]
Said et al.	*Lawsonia inermis* (henna)	Antibacterial	[64]
Selvam et al.	*Santalum album* (sandalwood)	Antibacterial and antioxidant	[65]
Sharifi-Rad et al.	*Lallemantia royleana* (balangu)	Antibacterial, antifungal, antioxidant, anti-inflammatory, anti-arthritic, and cytotoxicity	[66]
Subha et al.	*Carica papaya* (papaya)	Antibacterial	[67]
Taipe Huisa et al.	*Euterpe oleracea* (açaí palm)	Antibacterial and toxicity	[68]

Another strategy that has been explored is the use of support materials, thus achieving a controlled release of the supported AgNPs delivering lower and constant concentrations of AgNPs. These support strategies have been reported to present lower toxicity than free AgNPs [69] as well as greater bioactivity, since free AgNPs tend to aggregate and form larger particles that are less active than smaller nanoparticles [70]. Thus, various supports have been proposed for AgNPs such as dextrins [71] or polysaccharides like gelatin [72] or pectin [73]. Clay minerals have numerous advantages (e.g. non-toxic nature, natural abundance, low price, and high absorptive capacity, [74]) that have made them very attractive and desired support materials, having thus described the support of AgNPs in clay minerals such as montmorillonite [75] or palygorskite [76].

4. CURRENT LIMITATIONS OF SILVER NANOPARTICLES: WHAT ARE THE NEXT STEPS?

Nowadays, the study of the bioactivity of AgNPs seems to have as its final objective the development of therapeutic strategies capable of causing an impact on human health. Thus, the exploration of the beneficial effects of AgNPs in the healing of infected wounds [77] and burns [78] has allowed the development of marketed products impregnated with AgNPs, such as wound dressings [79] or central venous catheters [80]. However, medical applications seem to have plateaued at this point. In research that increasingly demonstrates the activity of AgNPs in pathogens that cause serious infections such as urinary tract infections, pneumonia, or even bacteremia, it is surprising that only topical administration products have been developed, a route whose bioavailability is limited [81] and they would not be effective in such infections (unless local administration was carried out, which has not yet been studied and would be highly invasive).

A similar limitation can be found in the antitumor applications of AgNPs. Indeed, it has been reported that AgNPs can cause apoptosis in cancer cells [82]-[84], but antitumor activity implies more than that. Firstly, it should be highlighted that these types of experiments are carried out on cell lines, which by definition are cancer cells or stem cells because otherwise there is no way to immortalize cell viability. It would be interesting to carry out these experiments on tumor cells extracted from patients. Secondly, an antitumor agent should not only mediate apoptosis of tumor cells, because tumors have components other than cells, like blood vessels. Some studies have suggested that AgNPs can reduce tumor angiogenesis, but the mechanisms are not entirely understood [85]. The immune system and the characteristics of its response to the tumor are also key to antitumor treatment. The study of the immune response involves the description of the tumor microenvironment, for which animal models must be used. For example, Garcia et al. [86] proved that AgNPs induce non-immunogenic tumor cell death using C57BL/6 and BALB/c mice, but in general few studies carry out *in vivo* experiments, and the use of animal models is essential to allow the AgNPs to be used as an antitumor treatment in cancer patients. These *in vivo* studies would also generate greater knowledge of the histological toxicity of AgNPs beyond cytotoxicity. It has been reported that AgNPs can induce neurotoxicity in mice [87], but the effect on other organs is not fully known, nor is the impact on human physiology [88].

Finally, future research should not only focus on human health but also consider the possible environmental impact that AgNPs can cause. In an increasingly connected world that seeks to be sustainable, it is not surprising that there is growing awareness that AgNPs can cause damage to the environment that goes beyond their action [89]. Thus, it has been seen that the mining and refining processes that take place when extracting silver are the most determining factors in environmental damage, but the emissions, energy or water spent on the different synthesis methods should not be ignored either [90]. Consequently, some studies have focused on understanding the effects that all processes can have on various ecosystems, such as the aquatic environment [91] or the soil microbiota [92].

As a result of this growing concern about the harmful effects of AgNPs on public health, numerous institutions across the European Union and the United States are focusing their efforts on agreeing on regulatory frameworks and guidelines for the safe use of this nanomaterial [93]. Thus, for example, the use of nanomaterials in cosmetic products [94], agrobiotechnology and food [95] and even in the development of therapeutic strategies in humans [96] has already been regulated. This effort by European and American institutions to create regulatory frameworks demonstrates the direction that future research should take: developing AgNPs that are friendly to both human health and the environment that can broaden the current spectrum of their applications to become strong therapeutic strategies.

5. CONCLUSIONS

Although the bioactivity of AgNPs is well known, research seems to be stuck in *in vitro* experiments. It is therefore necessary to go further, using new support strategies and *in vivo* models to ensure that one day this nanomaterial can reach the patient. To this end, it would be interesting for chemistry, environmental engineering, and other groups to work in an interdisciplinary manner together with biomedical research groups, both basic science and translational research, to explore these new strategies and bring AgNPs to the clinic.

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Conflicts of Interest

The authors declare no conflict of interest.

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