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Toward Synthesis-derived Applications of Silver Nanoparticles

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Abstract

This paper aims to review the challenges, toxicity, and routes of synthesis and usage of silver nanoparticles in different medical applications but also highlighting their sustainability from both medical and environmental issues. Regarding their toxicity, it is known that silver nanoparticles can destroy over 650 microorganisms comparing with antibiotics.

Supplementary, will be presented in a comparative manner some conventional synthesis routes (physical and chemical methods) and green synthesis routes using plant extracts. The approach using plant extracts have various advantages comparing with physical, chemical and microbial synthesis methods because there is no need to use chemicals, wasteful purifications and high energy requirements. The main focus in "*green nanotechnology*" was to use either biological micro-organisms or plant extracts which are an alternative to the classical chemical and physical methods.

An important issue that is discussed in the paper is the potential toxicity of silver nanoparticles that may have on human health or on the environment, which powerfully indicates that, the usage and removal of silver nanoparticles must be carefully examined. Also, it needs to focus our attention on the dismissal of silver nanoparticles into the environment and especially in water systems, fact which suggests that this issue must be fully understood and apply accordingly the law.

Keywords: silver nanoparticles, synthesis derived applications, biomedical applications, toxicity

Introduction

Nanotechnology is increasingly exploited in science and technology and has become a part of modern technology, which, nowadays, can be considered "a key technology of 21st century" [1]. Nanoscience and nanotechnology involve the synthesis, assembly, manipulation and application of the materials characterized by at least one size in the nanometric range, some of these nanomaterials being found in products available in our daily life. Nanoparticles are small sized materials with sizes ranged between 1 and 100 nanometres and due to their very small size lead to a high surface area, the reactivity increases considerable comparing with the bulk materials and many times even the physical properties are strongly changed. Due to their improved chemical and biological reactivity they may easily interact with cells and micro-organisms inducing or enhancing existent properties. Metal and metal oxide nanoparticles are extensively evaluated in medicine, environmental protection, energy, electronics, etc. Silver nanoparticles (Ag NPs) are studied for their applicability in biomedical applications [2, 3] (Figure 1) because of their antibacterial, antifungal, antiviral and anti-inflammatory activity [4, 5]. Also, figure 1 is illustrating some diseases that occur in human body along with the reliable biomedical applications of nanoparticles which could bring a great improvement in human health. Silver nanoparticles have been widely used in diagnosis [6], treatment [3], drug delivery

[5, 7], developing medical devices [1, 8], wound dressings [2, 5, 9, 10], medical textiles [6, 8, 11, 12] or contraceptive devices [5] as well.

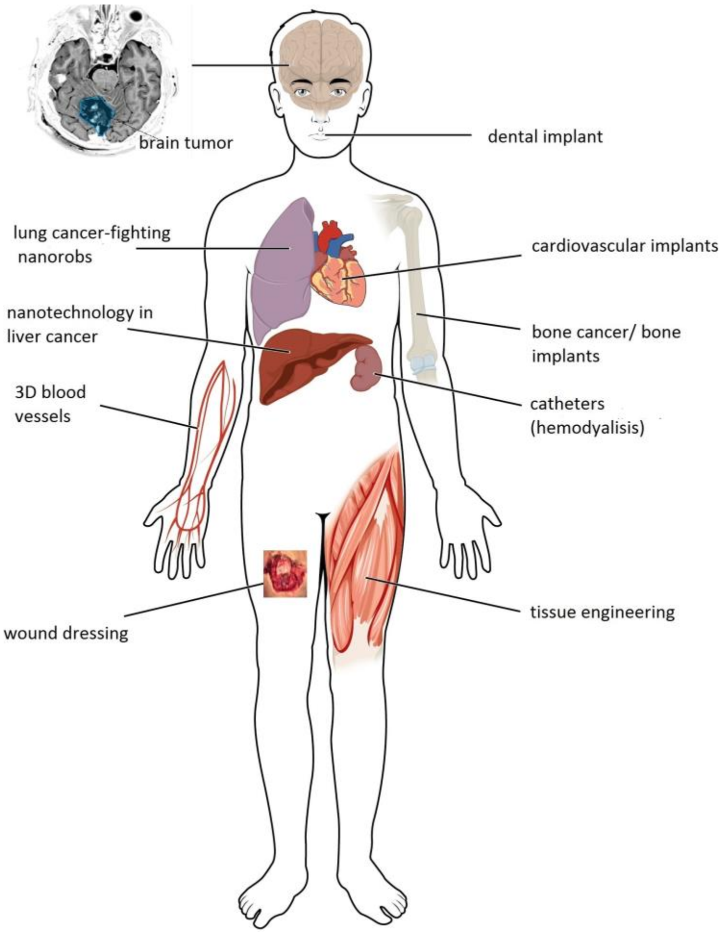

Figure 1. Biomedical applications of Ag NPs – an overview

Based on the recent studies, the necessity to make further investigations and evaluate the toxicity and release of silver in aqueous environmental as well as the release and penetration in contact with skin, have been highlighted as a mandatory step in establishing the opportunity of using these colloids in medical and environmental applications. One of the studies was made on wastewater biofilm which contained planktonic bacteria and due to the antimicrobial effect of silver nanoparticles it can disturb cells and communities' functions and functionalities. For example, the released of Ag^+ ions and also Ag NPs can interact with enzymes (usually via the thiol groups), can cause DNA inactivation and could cause a non-culturable state which will conduct to the death of the cells, even in biofilm state [5, 13, 14].

When silver nanoparticles or agglomerated particles get into the water systems it must be developed new modalities to overcome the possibility of pollution. Also, the oxidation rate is important because Ag^+ ions are also biologically active and must be considered when discussing about the overall toxicity. In fact, the speciation of silver in aqueous solution is very complex, silver ion being able to form a wide range of complexes while metallic silver surface can absorb a wide range of molecules. By any meanings, the risk of silver nanoparticles to get into the aqueous systems must be comprehended [15, 16]. Due to the fact that Ag NPs have antimicrobial application, it also can be useful for water purification [3, 17].

Zhang and Chinnapongse [18] have studied the behaviour of silver nanoparticles in different aqueous conditions. They have focused their studies on the transportation of silver nanoparticles in the porous media and on the comprehension of their potential environmental risks. From the current information on silver nanoparticles it is known that 15% of the total silver that was released into water in the EU came from biocidal plastics and textiles [19, 20] so, high environmental risks has to be considered. Moreover, many synthesis protocols involve wet synthesis routes which additionally increase the risks of water contamination.

Since the development of tuneable silver nanoparticles, the silver-based products is constantly growing, it has become a necessity to comprehend its biological interactions and their toxicity [3, 5]. This review discusses silver nanoparticles synthesis methods, especially green synthesis from plant extracts, properties, and emerging medical applications [5, 8]. Finally, recent advances concerning the toxicity of silver nanoparticles also are described. It has been already reported that the silver nanoparticles, in small concentration are harmless for human cells but considered biocides against bacteria, fungi and viruses and the only negative effect for human health is skin discoloration [3, 21]. Products containing silver nanoparticles can be found in pharmaceuticals [9], textiles [6, 11, 12], electronics [8, 22], food packages [22], cosmetics [9] and medical devices [1, 8]. Because of these issues, it has appeared the need to consider the possibility that may have effects on human health in any possible way [23]. Given its many uses in industry, in medical applications or in water disinfection the silver leakage, long term uptake / bioaccumulation and toxicity should be carefully analysed at both short and long-term [4, 5, 24]. The purpose of this review is to identify the exploitation of silver nanoparticles in medical applications and to examine their effects on the human health and the environment.

Synthesis routes of silver nanoparticles

Conventional synthesis routes of silver nanoparticles

It is well known that some of the processes which concern the synthesis of nanomaterials use toxic substances and involves high amount of energy that can generate potential toxicity. Therefore, the need to create clean, nontoxic and environmentally friendly methods for synthesis of different kind of nanoparticles has been appeared and generally accepted as a necessary precondition [5].

Silver and gold are among the most studied metal nanoparticles due to their potential use in medical treatment; lately, ZnO -NPs have been reported to have non-toxic effect to human cells, due to this aspect appeared the need to use it as antibacterial agent, being lethal to microorganism and having good biocompatibility to human cells [25]. Also, ZnO can be considered as an environmental friendly antimicrobial agent [26].

Silver nanoparticles, "*a wonder of modern medicine*" can fight against over 650 microorganisms comparing with the most antibiotics that are active against a much lower number of micro-organisms. Metal nanoparticles have been studied for decades because of their optical [3, 8], electronic [1, 8], magnetic [1, 3, 6], antimicrobial [2, 10, 11, 16, 27] and wound healing [5] properties. Due to their multifunctionality, large amounts of metal nanoparticles are needed and for their synthesis multiple methods were proposed and continuously are improved from the point of view of their activity but also synthesis cost, long-term stability, environmental impact, etc [28, 29] . Metal nanoparticles can be prepared by two physical or chemical routes.

The *physical route* employs processes like e*vaporation/ condensation* and *laser ablation*. The evaporation/condensation method uses a furnace tube under atmospheric pressure to produce metal nanoparticles. Laser-assisted processing is described by the laser ablation of metals in solution without chemical reagents, which leads to pure silver colloids. As a result, the silver evaporates and is condensed in water, where spherical nanoparticles having 20-30 nm of colloidal silver are obtained, usually in aqueous solution [5]. The characteristics of the metal

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particles formed and the ablation efficiency mainly depend on the wavelength of the laser scattering the metallic target, the duration of the laser pulses, the laser fluency, the ablation time duration and the effective liquid medium [30]. The main factor is that the size of the nanoparticles has been found that increases the laser energy and is generally smallest for fluencies not too far above the laser interruption. As well the laser fluency, the number of laser shots influences the concentration and the morphology of metal particles released in the liquid. Moreover, nanoparticles can be modified in size and shape due to the interaction with the laser light; the development of nanoparticles by laser ablation is influenced by the surfactant shell. The size of the nanoparticles produced in a high surfactant solution is smaller than those produced in a low-content surfactant solution. Thus, there is one benefit in comparison with the conventional method for preparing metal colloids which is the absence of chemical reagents in the solution and the produced pure silver colloids [31].

The other route is the *chemical method*, where the metal ions in solution are reduced in conditions favouring the subsequent formation of small metal individual particles, clusters or aggregates [31]. Silver nanoparticles can also be synthesized in a two-phase water-organic system. In this process uniform and controllable nanoparticle are produced, with a sharp size-distribution. The system contains a metal precursor and a reducing agent that are separated into the two phases. The interaction of the precursor /reducing agent occurs controllable, the intensity of interphase transport between the two phases can be controlled and subsequently the reducing process is highly controllable. The surface of the formed silver nanoparticles could be contaminated by the surfactants and organic solvents and the removal of surfactants and organic solvent is mostly time-consuming and expensive [5]. Silver nanoparticles can be prepared by micro-emulsion conditions. The separation of silver nanoparticles in two-phase aqueous organic systems is based on the initial division of reactants in two immiscible phases. The succeeding interaction between the metal precursor and the reducing agent is controlled by the interface between the two liquids. The metal clusters formed at the interface are stabilized, due to their surface coated with capping molecules from the non-polar aqueous medium and transferred to the organic medium by the inter-phase transporter. This method allows preparation of highly uniform and size controllable nanoparticles [31].

The preparation of silver nanoparticles through chemical reduction takes place in a stable, colloidal dispersion in water or organic solvents. The most common reduction agents used are borohydride, citrate, ascorbate or *in situ* generated elemental hydrogen. The reduction of silver ions in aqueous solutions, usually lead to the formation of colloidal silver with particles having several nanometres. So, reducing different complexes of silver ions conducts to the preparation of silver atoms followed by agglomeration into oligomeric clusters which will eventually lead to the formation of colloidal silver particles. Other studies showed that using a stronger reducing agent such as borohydride induces the formation of smaller particles. Also, using a weaker reducing agent such citrate showed a slower reducing rate, but with size distribution far from narrow. For instance, it is highly critical to use protective agents to stabilize dispersive nanoparticles during nanoparticles formation. The most common process is to protect the nanoparticles with agents that can be absorbed or combine on the nanoparticle surface, avoiding their agglomeration. For instance, Olivera *et al.* [32] adapted dodecanethiol-capped Ag NPs, based on the Brust procedure [33] using dodecanethiol as capping agent of silver nanoparticles which is based on a phase transfer of Au^{+3} complex from an aqueous to organic solution in a two-phase liquid–liquid system; this procedure is followed by a reduction with sodium borohydride in the presence of dodecanethiol as stabilization agent, avoiding their aggregation and making them dispersible in certain solvents. Through this process, it was showed that changing the synthetic parameters could lead to dramatic modifications in nanoparticle structure, average size and size distribution [31].

Green synthesis of silver nanomaterials

Green synthesis of silver nanoparticles usually belongs to the chemical route of synthesis and can be separated into five methods: *biological* methods, *polysaccharide* method, *irradiation* method, *Tollens* methods and *polyoxomerales* methods. The synthesis of silver nanoparticles in biologic method happens after reduction with microorganism extracts. Preparation of silver nanoparticles using polysaccharides and water as a capping agent is known as polysaccharide method. Sometimes polysaccharides act as both capping and reducing agent. Silver nanoparticles are prepared through various irradiation methods such as formation of silver nanoparticles of various size and shape by laser irradiation of silver salt and proper surfactants. Silver nanoparticles can also be fabricated by Tollens methods and polyoxomerale methods. Green synthesis process via the biological route is shown in figure 2 [3, 34].

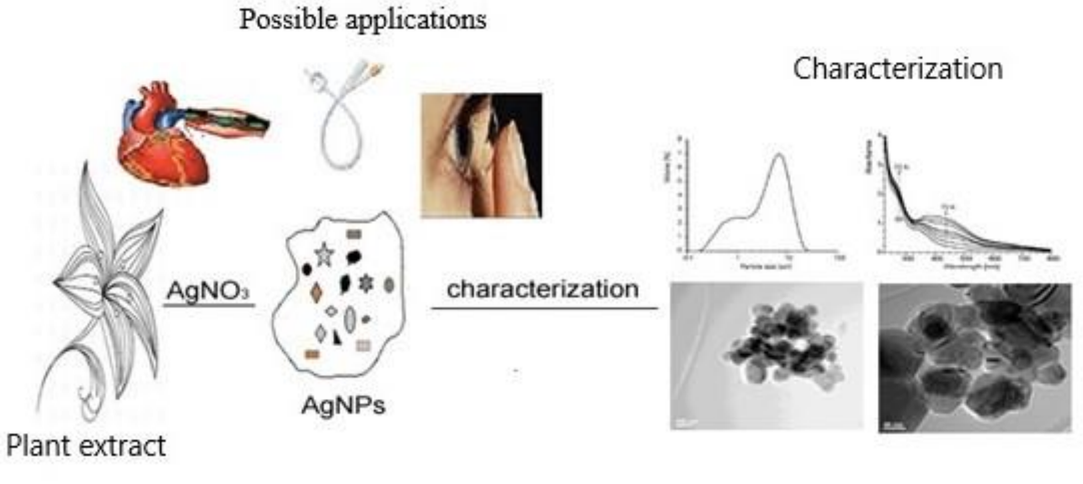

Figure 2. Green synthesis process of silver nanoparticles by using plant extracts

In biosynthesis process, at different concentration of silver nitrate, stable colloidal suspensions with spherical silver nanoparticles with diameter ranging between 0.5 and 150 nm were produced. Some of the synthesis routes of silver nanoparticles uses *plant extract* instead of micro-organism due to simplicity, attractiveness, user friendly, economical and fast approach [35]. The approach has various advantages comparing with the physical, chemical and microbial synthesis routes because in this process there is no need to use harmful chemicals, wasteful purifications and high energy requirements. Moreover, the composition of these extracts usually contains both reducing agents as well as capping agents and reduction and stabilisation occurs in one step [22]. By short, green synthesis is an eco-friendly and cost-effective alternative to classical physical and chemical methods. Plants extract are the most conventional reducing agents in green synthesis. Moreover, certain extracts exhibit strong biological activity such as antimicrobial, anti-inflammatory, antitumoral, etc. potentiating the biological activity of the silver colloids as presented in Table 1. Usually, in aqueous solutions silver ions reduces and produces colloidal silver. In crystallization route, Ag ions are reduced to Ag atoms which then grow into oligomeric clusters. Finally these clusters assist in developing the colloidal Ag particles [3, 36].

Table 1. Plant extracts used for silver synthesis and their potential activity.

Plant extracts	**Potential activity**	**Reference**
Alternanthera dentate – leaves extract	Antibacterial & antimicrobial	[37]
Acorous calamus – rhizome	Antioxidant, antimicrobial, anticancerous	[38]
Abutilon indicum – leaves extract	Antibacterial, antimicrobial	[39]
Cymbopogan citratus – leaves extract	Antibacterial, antimicrobial, antifungal	[40]
Thevetia peruviana - latex	Antimicrobial	[41]
Vitis vinifera – fruit extract	Antimicrobial, antibacterial	[42]
Musa paradisiacal – peel extract	Antimicrobial	[43]
Tribulus terrestris – fruit extract	Antimicrobial	[44]
Cocous nucifera – inflorescence extract	Antibacterial	[45]
Pistacia atlantica – seeds extract	Antibacterial	[46]
Citrus sinensis – peel extract	Antibacterial	[47]

This "*green nanotechnology*" has already been using either biological micro-organisms or plant extract which are an alternative to the classical chemical and physical methods [48-50].

Many experiments on marine microalgae, fungi and bacteria, *Amphora sp*, mangosteen extract, aqueous extract of *Citrus limon*, *Coleus aromaticus* leaf extract, olive oil extract have been made; in many of these studies the biological materials were used to reduce the silver ions to nanoparticles [51-61]. Nanomaterials may guarantee solutions to medical, technological or environmental issues, but it is strongly recommended that these nanoparticles to be developed through "green" synthesis methods in order to avoid the negative environmental issues. The principles of green chemistry affirm that needs to minimize the use of unsafe products and maximize the efficiency of chemical processes [62].

Since antiquity, it has been highlighted the need to study new effective antimicrobial agents, such silver salts or nanoparticles that has antibacterial effects and could be used for the treatment of the various medical diseases such as mental illness, nicotine addiction, gastroenteritis and infectious diseases like syphilis and gonorrhoea [63-65]. The application fields were drastically extended once with the discovery of their broad activity against the most classes of the hazardous microorganisms. Thus, silver nanoparticles are currently exploited in many applications as presented in Table 2. The following table presents expected applications of silver based active agents and their derived compounds. Some of the important applications include medical applications of silver nanoparticles mainly loaded with different polymers that exhibit low cytotoxicity and hemocompatibility. Table 2 highlights some modified silver nanoparticles with antimicrobial properties with application in medicine and textile industry / antimicrobial clothing but also some other applications that worth mention is presented in this table being related to environmental impact, food safety and energy producing.

Table 2. Silver based active agents and their derived applications

Crt. No.	**Active agents**	**Expected applications and references**
Medical applications		
1	Silver nanoparticles (Ag NPs) loaded in chitosan/ gelatine blend	Ag NPs-containing chitosan/gelatine (CS/G) polymers exhibit strong antibacterial activity against *Staphylococcus aureus* strains and *Escherichia coli* strains, limited cytotoxicity, good bond strength with metal substrate and good biodegradability [66]. It is also important to mention that the initial burst release of Ag ions prevent the initial adhesion of bacterial strains while exhibiting relatively low cytotoxicity to healthy cells creating the premises of reduce implant-associated infections. Also, these formulations can be used in wound dressing, for prevent or even to eradicate infections [67].
2	Silver nanoparticles modified with polydopamine and loaded into hydroxyapatite (Ag@pDA@HAp-NPs)	Silver nanoparticles may induce severe cytotoxicity and limited hemocompatibility when used in suspension. That is the reason because in most applications the surface of the silver nanoparticles is modified by adequate capping agents. Silver nanoparticles modified with polydopamine and loaded into hydroxyapatite was designed for bone tissue engineering, the surface modification of the silver nanoparticles considerable reducing the cytotoxicity and improving the hemocompatibility while silver release was of ~80% in first day – highlighting good antimicrobial activity against *E. coli* and *S. aureus* followed by a slow release for several days [68].
3	Silver loaded magnetic core@shell structures (Fe_3O_4@PTA@Ag)	Ag nanoparticles (NPs) conjugated onto magnetite nanoparticles through a tannic acid-metal polymer (PTA) intermediary layer exhibit the bactericidal activity suitable for water disinfection [69]. Similarly, copper, gold, and silver decorated magnetic core-polymeric shell nanostructures can be designed for destruction of pathogenic bacteria such as Gram-negative and Gram-positive bacteria [70, 71].

4	Silver@carbon nanocomposites	The multiple-Ag-nanoclustes-C-shell nanocomposites were produced from graft carbon dots (CDs) with silver nanoparticles (AgNPs). The resulting hollow multiple-Ag-nanoclustes-C-shell nanocomposites (Ag@C) highlight strong bactericidal effect against both gram-negative and gram-positive bacteria [56], and limited cytotoxicity against hamster ovarian cells [72, 73]. Another multifunctional material, Fe_3O_4@carbon dot/Ag (Fe_3O_4@C-dot/Ag) nanocubes (NCs) presented catalytic properties [57].
5	Silver-coated gold nanoparticles (Au-Ag NPs)	Ag NPs have antibacterial properties, however Au NPs are biocompatible and easy to prepare, and Au-Ag NPs were fabricated through Ag enhancement, where Au nanoparticles acted as nuclei for precipitation of Ag forming a core-shell structure immobilized onto a cellulose membrane when treating with heat. The Au-Ag NPs resulted in having nanoparticles of ~15nm immobilised on cellulose paper and exhibit excellent antibacterial activity against *E. coli JM109* and created the perspectives of using it as food packaging, clothing, wound dressings, and other personal care products [74].
6	Nitroxide-coated silver nanoparticles (N-Ag NPs)	Nitroxide-coated silver nanoparticles were embedded into the polystyrene by thermoforming at 140^0C. The antimicrobial activity was proved on *Pseudomonas aeruginosa* (Gram-negative representative) and *Staphylococcus aureus* (Gram-positive representative) as pathogenic bacteria. Polystyrene can be used in production of packages, including those for food and pharmaceuticals, numerous consumer goods, housing electronic equipment, inner lining of freezers and refrigerators, foam insulation boards, surgical instruments, dental tools, dressing materials, prosthesis, etc. In all these applications, the development of antimicrobial polystyrene is highly recommended while silver nanoparticles are a one of the best choice in inducing the desired antimicrobial activity [75-81].
7	Silver nanostructures coated with silica Ag NPs@ SiO_2	Silver nanostructures coated with silica can be obtained by various routes, one presented by Gonzalez-Castillo *et al*. [82] involve a three-steps methodology combining assisted laser ablation and redox reaction, the properties of the core@shell structures being controlled by laser pulse energy, ablation

		time, concentration of silver and gold salts (and if both silver and gold are used then Ag$^+$/Au^{3+} ratio). The main advantage of coating silver nanoparticles with porous silica is related to the better stability while silica shell provides inertness and inequity character which entails possible use in biomedical applications.
8	Silica coated with silver nanostructures (SiO_2@Ag NPs)	Silica coated with silver nanostructures act as a platform with potential use in nanomedicine, including cancer treatment. Based on the experimental data provided by Mateis *et al.* [83], silver release is promoted by acidic conditions, characteristic to tumour environment, so targeted action can be obtained. Using these SiO_2@Ag NPs core@shell structures a combined therapy is assured by the delivery of the silver ions along with the delivery of bioactive compounds encapsulated into the silica core. These formulations are of high interest because the mesopores can host a wide variety of biological active agents inducing new properties or enhancing the existent, antimicrobial activity [84, 85].
9	Vancomycin Derivative Modified Silica-coated Silver Nanoplate	Complex multi-layered structures based on silica shell coated Ag NPs as nanoplates active cores were modified with porphyrin-vancomycin (Por-Van) derivative was developed in order to fabricate AgNPl@SiO_2-Por-Van composite to induce Antimicrobial Photodynamic Therapy (aPDT) of Vancomycin Resistant enterococci bacterial strains (VRE) and, supplementary, able to be used as imaging agent in Surface-Enhanced Raman Scattering [86].
Antimicrobial clothing		
10	Gallic acid modified silver nanoparticles (GA@Ag NPs)	Antimicrobial leather with durable activity due to the high versatility of linking Gallic acid modified silver nanoparticles to the surface of the leather [87]. Similarly, tannic acid modified silver nanoparticles can be obtained and used for antimicrobial purposes [88].
11	Citrate modified silver	Various textiles were functionalized by silver to induce antimicrobial surfaces. After the

	nanoparticles (CA@Ag NPs)	functionalization, the Ag NPs-fabrics exhibited antimicrobial properties in the order silk > linen > nylon > PET. The morphology of the silver nanoparticles is substrate-dependent, but also the content of silver differs considerably, the highest amount of silver can be found on silk (12.05±0.41g Ag NPs/kg) followed by PET (5.77±0.21g Ag NPs/kg), linen (4.37±0.89g Ag NPs/kg) and finally nylon (2.65±0.05g Ag NPs/kg) [89].
Energy applications		
12	Ag@SiO$_2$ nanospheres deposited onto Indium tin oxide layer	Ag@SiO$_2$ nanospheres were designed to obtain Plasmonic Organic Solar Cells. The optimisation was done considering the periodicity of the array, the Ag core diameter, the active layer thickness, the shell thickness, and the refractive index of the shell materials. Based on the study realized by N'Konou *et al.* [90] it was found that the optimal periodicity of the Ag@SiO$_2$ array is dependent on the size of Ag core. They found that the use of Ag@SiO$_2$ nanospheres (50 nm) can improve the optical absorption with 24.7% (comparing to the similar structure without Ag@SiO$_2$ nanospheres).
13	Silver nanoparticles and nanostructured active materials such as metal hydroxide, hydrates or sulphides	Wearable supercapacitors with core@shell hierarchical structure based on silver-coated textile and nanostructured active materials were obtained using metal hydroxides (e.g. Ni(OH)$_2$, Ni–Co layered double hydroxide (LDH)), hydrates (e.g. NiMoO$_4$ hydrate), and sulphides (e.g. Ni(Fe)Co$_2$S$_4$) with three typical nanostructures of a 1D nanotube array, a 1D nano rod array, and a 2D nano sheet network. As a general conclusion of the work published by Li *et al.* [91], both the nature of the active materials but also the morphology is critical factors affecting the performances of the wearable super capacitor.
Environmental applications		
14	Fe$_3$O$_4$@nSiO$_2$@mSiO$_2$/Pr-	The core@shell nanoparticles with a superparamagnetic iron oxide core (Fe$_3$O$_4$), middle nonporous

	Imi-NH_2·Ag NPs core-shell microspheres	silica shell ($nSiO_2$), and organo functionalized mesoporous silica ($mSiO_2$) were synthesized and evaluated for retaining Ag NPs onto the nanocomposite. The Fe_3O_4@$nSiO_2$@$mSiO_2$ was functionalized with 2-amino ethyl-3 propyl imidazolium bromide resulting magnetic core-shell mesoporous silica nanoparticles, Fe_3O_4@$nSiO_2$@$mSiO_2$/Pr-Imi-NH_2 and afterwards was embedded with silver nanoparticles. Fe_3O_4@$nSiO_2$@$mSiO_2$/Pr-Imi-NH_2·Ag NPs core-shell microspheres are highly efficient catalysts in the aqueous reduction of nitro arenes highlighting improved catalytic activity and facile catalyst recovery. These systems can be exploited in the environmental protection being able to reduce aromatic nitro-derivatives to aromatic amino-derivatives with much lower negative environmental impact [92].
15	Fe_3O_4@SiO_2@Ag@Ni trepang-like nanocomposites	The analysis started from Fe_2O_3 nanorods coated with a layer of silica, and after reduction in 10% H_2/Ar atmosphere, the magnetic Fe_3O_4 was obtained. The Fe_3O_4@SiO_2@Ag@Ni trepang-like nanocomposites were obtained by coating the Fe_3O_4 nanorods previously obtained with silica followed by final deposition of Ag@Ni core@shell on the lysine modified surface of Fe_3O_4@SiO_2. It is worth to mention that Fe_3O_4@SiO_2@Ag@Ni trepang-like nanocomposites exhibit remarkable catalytic efficiency toward the degradation of Rhodamine B at room temperature and this activity is maintained even after 6 cycles. Moreover, the magnetic core allow an easy separation / removal of the catalytic system [93] therefore the negative environmental impact being low.
16	Ag-coated Fe_3O_4@TiO_2	The Ag-coated Fe_3O_4@TiO_2 photocalysts have a core-shell structure formed by Fe_3O_4 core and a nano-shell of TiO_2 with Ag nanoparticles. The Ag-coated Fe_3O_4@TiO_2 magnetic photocatyst exhibited good photocatalytic activity in the degradation of Rhodamine B under visible light. Chlorophenols are common pollutants from water which can be destroyed using adequate recyclable and renewable photocatalyst such as Ag-coated Fe_3O_4@TiO_2 [94].

Food safety		
17	Au@Ag Core-Shell Nanoparticles	Food quality and safety are of increasing interest, worldwide. Extensive and many times irrational use of chemicals (pesticides, insecticides, antibiotics…) lead to food contamination and improved or novel detection methods should be developed. Au@Ag Core-Shell Nanoparticles can be used as enhancing agent to determine amitraz residue in milk because Au@Ag Core-Shell NPs induce a strong SERS signal at Au@Ag: amitraz ratio of 2:1. The linearity of Raman intensity (at $723cm^{-1}$) is in the range of $9.77x10^{-4}$ to $2.93x10^{-2}g/L$, the recovery of amitraz from milk was found to be between 81.7 and 100.5% while RSD was 2.61-5.51% [95, 96].
18	$Ag@SiO_2$ nanoparticles	The use of enzyme-based miniaturized fluorescence biosensor to detect paraoxon (metabolite of the insecticide called parathion), one of the most well-known neurotoxic organophosphorus compounds was developed by Kim *et al*. [97]. The biosensor was obtained by using PEG as a hydrogel entrapping acetylcholinesterase and quantum dots as fluorescence reporters. Metal-enhanced fluorescence ($Ag@SiO_2$ nanoparticles) was used to amplify the fluorescence signal, the signal increase being 5fold comparing with the system without $Ag@SiO_2$ nanoparticles. The presence of $Ag@SiO_2$ nanoparticles is important because assure a detection limit of $1.0x10^{-10}M$ (comparing with $2.0x10^{-7}M$ when no $Ag@SiO_2$ NPs is added).

2

The mechanism of action of nanoparticles is very important and differ depending on the nature and characteristics of nanoparticles [11, 13, 31, 98-104]. In the case of silver nanoparticles, the antimicrobial and anti-fungal activity is mainly assured by the produced Reactive Oxygen Species (ROS) which are altering the normal, intracellular functions of these micro-organisms while, most of the metal oxides (ZnO, MgO and CaO) are inducing a cellular wall destruction and consequently these microorganisms are losing their integrity. Other metal oxide nanoparticles can induce antimicrobial activity because of the photo-catalytic activity when exposed to visible or UV radiation. Such metal oxides are TiO_2 and ZnO. These nanoparticles are effective in aqueous suspension but also many applications are known where these nanoparticles are dispersed into the bulk materials or deposited onto various surfaces [102, 105-107]. The properties can be designed also by developing heterogeneous core@shell structures as 1D (particles), usually dispersed in aqueous suspension or deposited as 2D antimicrobial coating (film) [108, 109].

Advantages and disadvantages of different synthesis routes

Nanoparticles have multiple applications in aerospace engineering, nano-electronics, environmental remediation, medical healthcare and consumer products and lately silver nanoparticles ranged from disinfecting medical device, water treatment to bio-sensing and imaging applications. Many experiments indicated that different nanoparticles once after inhaled can deposit in the olfactory mucosa of the nasopharyngeal region and can gets to the brain through the olfactory nerve [110]. *In vitro* studies reported that silver nanoparticles produce toxicity to a variety of organs and leaving cells [111] but it was established that after a 28 day *in vivo* study, silver doesn’t affect neurological or respiratory system [5].

Complex materials based on chitosan–coated with silver nanoparticles showed that exhibit good antimicrobial activity due to the synergic activity of the both antimicrobial agents [112, 113]. Another application in which hydroxyapatite is doped with silver or loaded with silver nanoparticles in order to obtain antibacterial bone grafts showed promising results being active antibacterial grafting materials against gram-positive (*S. aureus*) and gram-negative (*E. coli*) bacteria [68]. Silver based materials have also environmental application; for water filtration fibrous materials based on silver nanoparticles and PVA or PAN were obtained and evaluated. Both materials were ideals for water filtration and sanitation and silver hasn’t been found in water, over the admitted level. From the many applications of silver one of the most significant for human health is related to the detection and treatment of various forms of cancer. Silver loaded hydrogels with curcumin (member of ginger family) exhibit excellent antimicrobial, anti-oxidant, anti-inflammatory and even anti-tumour activity as reported by different research groups [114, 115].

In his article, George J. Maass [116] from Colloidal Science Laboratories and senior scientific advisor at Purest Colloids Inc. reported that "the high biological effectiveness of colloidal silver does not persist in nature because the nanoparticles agglomerate as soon as they come in contact with the species from environment, especially from soil and water" and "once agglomeration occurs, the results is simply silver metal, a harmless metal which has existed in nature from the beginning of our planet" [116]. Unfortunately, these statements are not fully agreed in the scientific literature. Even if the agglomeration leads to the decrease of the toxicity and possibility of internalisation in cells, under different circumstances these agglomerates can break, and their initial toxicity is recovering. Also, the changes of the conditions can lead to a stronger oxidation and thus, the toxicity induced by the higher level of silver ions became important [117, 118].

Toxicity and challenges

Prime upcoming challenge would be the transition of laboratory use of silver nanoparticles to commercial application, including clinical applications. Researchers and scientists around the world focus their work to study nanoparticles synthesis, their properties and the derived applications. Even at low quantity, the silver nanoparticles could exhibit minor toxicity and could be very dangerous to the organs of the body. To overcome the difficult challenges that come along with the manufacturing of drug delivery systems, diagnosis and treating fatal diseases must be taken into the consideration the possible limitation of silver nanoparticles in some application due to aggregation and potential toxicity. A transition from *in vitro* to *in vivo* testing could be the only way to find out the mid- and long-term toxicity. Moreover, the *in vivo* behaviour can be strongly different comparing to that *in vitro* where no "*in vivo* specific mechanisms are available for the organisms". For instance, there are studies on burn patients that cause hypersensitivity, and some are harmful to specific cell lines. It was found that silver nanoparticles can be contaminated (oxidized) in air due to its high surface energy. This issue could be overcome by incorporating silver nanoparticles into biodegradable polymer matrix like chitosan, alginate, gelatine, collagen, etc. [119].

Silver nanoparticles may have toxicity over certain concentration and can cause serious health problem. Hence, it is necessary to focus our attention on the safe use of silver nanoparticles for applications involving humans or animals. *In vitro*, silver nanoparticles have shown cytotoxicity on different types of cells, including human peripheral blood cells, human alveolar epithelial cell, rat liver cell and mouse germ line cells. It has been found that bone cement containing 1% silver nanoparticles is not leading to cytotoxicity in mouse fibroblasts and human osteoblast cell line. This fact suggests that silver nanoparticles are ionized in the cells producing reactive oxygen species that leads to cell death. *In vivo*, silver nanoparticles can get into the human body during the exchange materials through the most important portals such as respiratory tract, gastrointestinal tract, skin, and female genital tract. Recent studies related to the silver oral administration to rats, has found that silver nanoparticles accumulates in blood, liver, lungs, kidneys, stomach and brain, but silver nanoparticles showed no genotoxicity after 28 days of oral administration of different doses of silver nanoparticles with size of 60 nm [5]. At lower size, the shape is also important, and the biological activity is strongly correlated with these factors. The shape, size and charge of the nanoparticles influence proteins that can be absorbed to the nanoparticles surface but if the nanoparticle size is greater than 15-20 nm, it is not considered an important parameter to determine its biological effects. For instance, rod shaped silver nanoparticles in the range of 40-100 nm presented extraordinary penetration in comparison to spherical and triangular particles. The cell wall penetration and thus the cell internalisation are strongly controlled by size and surface geometry and nature (functionalization agents) [120-122].

This sequence summarizes the molecular procedure of silver nanoparticles toxicity. This procedure explains that toxicity of silver nanoparticles is strictly connected to its transformation in biological and environmental medium and due to surface oxidation; silver ions release and interact with biological macromolecules. It is difficult to define what portion of the toxicity is from the ionic form and what portion is from the metalic-form. Silver NPs can be binded on the membrane proteins and trigger signalling route, which leads to cell proliferation. Ag NPs can also penetrate the cell through diffusion or endocytosis and produce mitochondrial dysfunction, generating reactive oxygen species (ROS) which lead to the damage to the proteins and nucleic acids inside the cell and finally the inhibition of cell proliferation. Another important reason for toxicity of Ag NPs is the interaction with both the ionic and metallic forms of the silver with sulphur-containing macromolecules like proteins because of the strong attraction of silver to sulphur [16].

The literature has concluded that silver nanoparticles shown intensive toxic effects upon some tissues and being ingested can induce neurological problems, kidney damage, stomach upset and skin irritation [123-125]. The increasing use of nanomaterials in our life has inevitably caused accumulation in different environments (water, soil and air) and to separate them we need to determinate the aggregation and stability, including tendency of transforming into different species. The approaches presented are necessary to detect the possibilities of the fields of nanotechnology to establish if has any risks for organisms including human beings [125, 126]. Pure silver nanoparticles were used by Kursungoz *et al.* [127] to evaluate the neurotoxicity on the rat hippocampal slices. Silver nanoparticles were distributed in the extracellular matrix and were taken inside the cytoplasm of the neutrons. Furthermore, it was found that only larger silver nanoparticles were taken into the neurons via phagocytosis. The silver nanoparticles produced via laser ablation showed that were toxic to the neural tissue [128] showed that neurons affected only the large nanoparticles by phagocytosis, fact that seems to be the main mechanism in silver nanoparticles neurotoxicity.

Another study investigated the potential of *T. viride* (MTCC 5661) to enhance the antimicrobial activity of biosynthesized silver nanoparticles (BSNP) in comparison to citrate stabilized silver nanoparticles (CSNP). Based on the results obtained, BSNP was able to penetrate bacterial membrane more easily than CSNP, which demonstrates the enhancement of antimicrobial efficiency of silver nanoparticles by reducing and modifying their surface with antimicrobial metabolites of cell free filtrate of *Trichoderma viride* (MTCC 5661) in comparison to citrate stabilized silver nanoparticles. So, this study affirms that biologically synthesized silver nanoparticles coated with antimicrobial metabolites of *T. viride* were more effective than their chemical counterpart in killing of pathogenic bacteria [129].

It is generally accepted that silver nanoparticles, as well as many other engineered nanoparticles alter the human and animal microbiota. This alteration is mostly associated with dysfunctions which are correlated with the size and shape of the silver nanoparticles (AgNC –

silver nanocubes and AgNS – silver nanospheres) [130-134]. Considering the most representative species of the microbiota it was found that *Clostridium spp.*, *Bacteroides uniformis*, *Christensenellaceae*, and *Coprococcuseutactus* were decreased in AgNC exposed group, whereas, *Oscillospira spp.*, *Dehalobacterium spp.*, *Peptococcaeceae*, *Corynebacterium spp.*, *Aggregatibacterpneumotropica* were reduced in AgNS exposed group. The main conclusion of the study is that, even at short-term exposure to AgNS or AgNC, important changes occurs from the point of view of behaviour and viability of the gut microbiota.

Conclusions

This review focuses on the synthesis methods, especially green synthesis from plant extracts, properties, medical applications, toxicity of silver nanoparticles and the possible impact on the environment. Some of the synthesis routes of silver nanoparticles use plant extracts instead of microorganisms due to simplicity, attractiveness, user friendly, economical issues and their fast approach but also because these extracts can assure, simultaneously, multifunctionality of the silver nanoparticles. The use of proper extracts can assure the necessary reducing agents but also capping agents or additional agents able to induce new biological activities or can enhance existent ones.

Researches affirmed that the synthesis of silver nanoparticles it was found that silver nanoparticles exhibit better antimicrobial activity when adequate natural extracts, metabolites, bacterial lines are chosen and improved internalization was found but, there are only limited papers dealing with this issue so, further confirmations are still necessary, both at short- and long-term level. Based on the statements described it can conclude that silver nanoparticles have an adverse impact on the environment. So, closer attention needs to be paid to the discharge of silver nanoparticles into the environment. Also, silver nanoparticles seem to bio-accumulate, which means that silver nanoparticle concentration will continue to increase over time in water sources. Hence it is strongly suggested that the use and disposal of silver nanoparticles need to be scrutinized.

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