ISSN: 2578-8760

Journal of Nanomedicine

Open Access | Review Article

A Review on Green Synthesized Silver Nanoparticles and Antibacterial Action: Usage in Dentistry

Katayoun Karami Shabankareh[1]*; Mohammad Behnaz[2]; Mohsen Dalband[3]

[1]Faculty of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[2]Dental Research Center, Research Institute of Dental Sciences, School of Dentistry, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[3]Department of Oral and Maxillofacial Surgery, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

***Corresponding Author(s): Katayoun Karami Shabankareh**

Department of Inorganic Chemistry, Faculty of Chemistry, Razi University, Kermanshah, Iran.

Email: senualkate@gmail.com

Received: Feb 10, 2023

Accepted: Mar 08, 2023

Published Online: Mar 15, 2023

Journal: Journal of Nanomedicine

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Silver nanoparticles; Green synthesis; Plant extracts; Dentistry.

Abstract

Metal nanoparticles (NPs) have the highest effectiveness among the most innovative nanotechnological applications due to their special action modes. For instance, Ag^+ ions are broad-spectrum antibacterial agents with the capacity of effective inhibition of the growth of fungi, algae, and bacteria. Nanoscale silver particles with a large surface-area-to-volume ratio (size below 100 nm) are significantly interesting because of their great antimicrobial actions against viruses, Gram-negative and Gram-positive bacteria.

Many in vitro research works have been conducted describing the antimicrobial activities of plant-mediated AgNPs against oral pathogens. During NP green synthesis process, not only the metal salts are reduced by biological molecules, but also they coat the produced NPs or act as in situ capping and reducing agent. It has been proved that silver NP is a promising compound that can be employed in dentistry because some researchers have used the strategy of incorporating antimicrobial substances in dental biomaterials. Hence, green process developed AgNPs can be a promising approach for producing antimicrobial agents against oral pathogens. Thus, in this review, recent researches regarding merits of various plant-mediated approaches for the synthesis of silver nanoparticles over traditional methods were collected. Then recent applications in various fields of dentistry were presented.

Cite this article: Shabankareh KK, Behnaz M, Dalband M. A Review on Green Synthesized Silver Nanoparticles and Antibacterial Action: Usage in Dentistry. J Nanomed. 2023; 6(2): 1061.

Introduction

Antibacterial resistance is currently a common problem, which is regarded as one of the globally complicated challenges in the health area. Discovering and synthesizing new biomedicines or finding natural alternatives is a demanding needs since it a significant priority that is highly requested in the current situation. Community and hospital-acquired infections are generated mostly by multidrug-resistant bacteria and these infections have become the most challenging condition in the world[1]. Besides, these multidrug-resistant bacterial pathogens have considerably increased the death rate. There are various research works suggesting the development of new multidrug bacterial resistance genes as a result of the inappropriate and immense use of antibiotics [1]. Therefore, discovering and developing new warfare plans is crucial for fighting against multidrug-resistant bacteria and reducing the widespread consumption of antibiotics for the treatment of microbial infections.

Generally, antibacterial materials are classified into three groups: organic, inorganic, and natural materials. There is low heat resistance in organic antibacterial materials that probably create bacterial drug resistance, while the range of application of natural antibacterial materials is limited. Inorganic antibacterial materials show better performance compared to organic antibacterial materials in terms of antibiotic resistance development in bacterial strains, heat resistance, and durability. Thus, recently, they have drawn considerable interest [2].

As a result of advanced research in nanotechnology, nanoscale objects have been developed with salient antimicrobial actions against multidrug-resistant pathogens, which suggest a platform for fighting against bacterial mutation arch [3,4]. Metal nanoparticles (NPs) have the highest effectiveness among the most innovative nanotechnological applications due to their special action modes [5]. Given that essential metals have microcidal lethal impacts (crucial for the life biochemistry in all organism fulling cellular functions) in excessive dose, and also effects of nonessential metals, even at small doses, traditionally it has been proved that using metals as antimicrobial agents is scientifically justified in this regard [6-8]. In some cases that there is tight bonding between metal ion and antibiotic structure (for example, bleomycin, bacitracin, albomycin, and streptonigrin), which manages the biocidal action [9]. In this case, they attach to the antibiotic molecule (for example, aureolic acids, quinolones, and tetracyclines) and no critical change is created in antibiotic structure while the activity is enhanced [10]. Considering the microcidal nature, the synthesis of metal NPs highly attracts nanotechnologists and researchers.

For instance, Ag+ ions are broad-spectrum antibacterial agents with the capacity of effective inhibition of the growth of fungi, algae, and bacteria [11]. IT has been shown that many inorganic NPs cause severe cytotoxicity, proving that it is possible to develop a novel generation of bactericidal materials [12]. Specifically, researchers have investigated silver NPs for their notable antibacterial action and creating the least damage to human cells [13]. As an example, effective antibacterial action has been observed in silver NP-coated silicon nanowires [14].

Nanoscale silver particles with a large surface-area-to-volume ratio (size below 100 nm) are significantly interesting because of their great antimicrobial actions against viruses, Gram-negative and Gram-positive bacteria [15,16] , as well as other eukaryotic microorganisms [17], in comparison with other nano-metals. Also, it indicates potential effects of these particles against multidrug-resistant and multidrug susceptible strains, like Pseudomonas aeruginosa, ampicillin-resistant Escherichia coli, vancomycin-resistant Staphylococcus aureus (VRSA), erythromycin-resistant Streptococcus pyogenes, and methicillin-resistant Staphylococcus aureus (MRSA). Because of their biocidal actions, various chemical and physical routes have been used for the synthesis of AgNPs. Moreover, it has been attempted to apply AgNPs to surface modification, fiber-grafting, coating, preparation of gels, etc. [18-21]. However, the drawbacks include use of toxic solvents (e.g., polyvinyl pyrrolidone, sodium dodecyl benzyl sulphate), use of toxic forerunner chemicals (e.g., potassium bitartrate, sodium borohydride, hydrazine, methoxy-polyethylene-glycol), and the emergence of toxic by-products through traditional roots (chemical and physical approaches) of silver NP synthesis. With scientific improvements, alternative environment-friendly routes were found for synthesizing metal NPs. There are a large number of works [22,23] focusing on the mechanisms and antibacterial performance of Ag-NPs. Counterparts [24] . Various studies have been carried out for indicating the impact of Ag-NPs shapes on their antibacterial activities. The number and status of surface plasmon resonance (SPR) peaks are subject to the Ag-NPs shape. For instance, a single scattering peak is presented by spherical particles. On the contrary, multiple scattering peaks are presented by anisotropic shapes, like triangular prisms, cubes, and rods, in the visible wavelengths since they have very localized charge polarizations at edges and corners [25,26]. Thus, it is challenging to achieve a size-tunable synthesis of Ag-NPs with extensive surface area and surface activity and poor stability, and a high aggregation capability [27,28]. Hence, researchers have discovered many forms of Ag-incorporated NPs, and it has been found that Ag-NPs immobilized on different organic and inorganic substrates increase and extend antibacterial properties [29].

Green synthesis of Ag NPs

Synthesis of AgNPs was achieved by biological extract in situ that reduced silver salts (Ag+) to metallic silver, Ag(0). During NP green synthesis process, not only the metal salts are reduced by biological molecules, but also they coat the produced NPs or act as in situ capping and reducing agent. Such capping is beneficial since it works multifunctionally; (i) preventing the NPs agglomeration, (ii) reducing the toxicity, [30,31] and (iii) enhancing antimicrobial action [32-35]. A synergistic impact of the capped bio molecules and metal NPs can be shown in case that these coating agents present antimicrobial action. Here AgNPs present action for their size and bio molecule over NP surface for its antimicrobial action. In many cases, it is the probable reason for the low antimicrobial action of NPs that are biologically synthesized. Therefore, for the green synthesis of silver NPs, the focus of the research is on synthesis of AgNPs by the use of bio molecules that have antimicrobial actions. In the past ten years, widespread studies have been conducted on biosynthesized Ag-NPs [36].

Ag-NPs have had antimicrobial applications because of their antimicrobial properties. As a result of such special properties of silver NPs, they can be easily used in such areas as pharmacy, nanomedicine, biomedical engineering, and biosensing. As discovered by Mittal, synthesis of metallic NPs with plant extracts was economical and eco-friendly, supporting different analytical approaches [37]. Besides the benefits, it should be acknowledged that there are also some problems related to the green synthesis of Ag NPs. The limited number of shape sizes and slow synthesis rate of NPs are among the main disadvantages of applying plant extracts for the synthesis of Ag NPs, and in comparison with conventional approaches, a low yield of secreted proteins is produced by plants. It is not possible to manipulate plants because of the choice of NPs either through genetic engineering or through optimized synthesis [38]. Various studies have published antimicrobial, antiviral, anti-rheumatic, bacterial, expectorant, diuretic, insecticide, and hypertensive activities for many natural products. Synthesis of biogenic NPs by the use of plant extracts with the aim of antimicrobial potency can have synergistic effects on organisms [39]. That is, varying by the ease of processing and productivity for being automatically safe with such a single-phase approach for large-scale NP synthesis, the biological synthesis of silver NPs could have many auspicious dimensions. The number of studies overviewing Ag-NP antibacterial activity and its biosynthesis is limited. The surface morphology, shape, and size of Ag-NPs are significant factors that determine their properties. There is a link between the antibacterial activity of Ag-NPs and the release and oxidation of Ag+ ions into the environment. Thus, it is regarded a significant antibacterial agent [40]. It is projected that Ag-NPs have a high fraction of surface atoms and a large surface area to volume ratio in comparison with pure silver metal, resulting in great antibacterial activity [41]. Besides, as a result of the small size of Ag-NPs, the diffusion in the cell membrane is easier and the bacterial cell's intercellular processes are altered. Green-synthesized Ag NPs are mostly studied for cancer therapy or their antibacterial characteristics. Studies in recent years have demonstrated that it is possible to synthesize Ag-NPs with 17-29 and 38-72 nm diameter ranges using Chrysanthemum Indicum or Acacia Leucophloea extract [42,43]. These samples both have shown noticeable antibacterial effects. In a similar way, Ag- -NPs were synthesized using Ganoderma Neojaponicum Imazeki that can be employed as chemotherapeutics against breast cancer cells [44].

Ag-NPs have been generated by green synthesis using various biological sources, such as algae, fungi, and plants **(Figure 1)**.

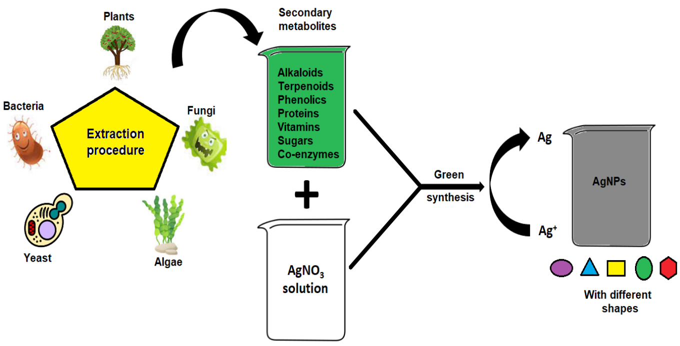

Figure 1: Schematic representation of the procedure for green synthesis of silver nanoparticles using various biological entities.

However, the general method is an herbal-mediated fabrication of Ag-NPs. Different green plants extracts, e.g., stem bio resources, leaf extracts, etc. have been utilized by these studies. Metal NPs (MNPs) with varying shapes and sizes have been synthesized using various methodologies. MNP synthesis is mainly realized by different chemical and physical approaches, including lithography, laser ablation, sol-gel method, electro-deposition, and chemical vapor deposition. Nevertheless, these are costly approaches and it has been reported that the products produced from them could harm the environment and human beings. These approaches are described in detail elsewhere [45,46]. Considering concerns and challenges regarding synthesis of MNPs using chemical and physical techniques, it has been attempted to develop cheaper and greener techniques for the MNPs synthesis. The MNPs have a more eco-friendly and cost-effective and biosynthesis in comparison with the physical and chemical techniques. In green synthesis approaches, first, natural compounds are extracted from plants or microorganisms, and then these extracts are used for the in vitro synthesis of the MNPs. The materials produced by plant extracts utilize one-step synthesis, are rapid, and do not necessitate complicated purification approaches [47]. Synthesis of MNP with the mediation of plant extracts is more cost-effective since plant extracts can be prepared readily and it is possible to use extracts from different materials of plants, like roots, leaves, stems, flowers, barks, fruits, vegetables, etc. in the synthesis [48,49]. Furthermore, plant-derived waste, including fruit peels, can be utilized for synthesis of MNPs. These plant materials are rich in secondary metabolites (amino acids, vitamins, enzymes, antioxidants, polysaccharides, proteins) and phytochemicals (for example, terpenoids, alkaloids, phenolic) acting as capping, stabilizing, and reducing agents within the MNPs synthesis, either individually or used together [50].

Green synthesis of Ag NPs using plant extracts

Plants have had widespread usage in contrast to microorganisms because phytochemicals of plants have higher stabilization and reduction [51]. Using Eugenia jambolana leaf extract, AgNPs were synthesized, which showed the availability of flavonoids, alkaloids, sugar compounds, and saponins [52]. The presence of carboxyl and hydroxylamine groups was observed in bark extract of Saraca asoca [53]. AgNPs were synthesized by the use of leaves of Rhynchotechum ellipticum, and the availability of flavonoids, alkaloids, polyphenols, carbohydrates, steroids, and terpenoids was noted [54]. AgNPs of 20–40 nm diameters were formed using hesperidin [55] . It was found that phenolic compounds of oleic acid and pyrogallol are crucial for reducing silver salt to for formation of NPs [56]. Pepper-leaf extract works as a capping and reducing agent in forming AgNPs of 5–60 nm [57]. Fruit extracts of Malus domestica functioned as a reducing agent. Besides, researchers have reported Vitis vinifera, 39 Andean blackberry [58], Solanum nigrum [59], Adansonia digitata [60], Nitraria schoberi [61], or various fruit peels for synthesis of AgNPs [62]. Also, previous studies have reported combinations of plant extracts [63]. Some other reductants that have been utilized for AgNO3 include soluble starch [64], polysaccharide [65], natural rubber [66], cinnamon, tarmac [67], 25 red apple [68], 25 stem-derived callus of green apple, egg white [69], coffee [70], lemongrass [71], black tea [72], Abelmoschus esculentus juice[73], Phyllanthus emblica [74], and Gracilaria birdiae [75] . In addition, Figure 3 indicates a general diagram that represents various parts of leaves of different plants, such as seed, peel, flower, fruit, root, bark, and stem, utilized in nano formulations. Green synthesis is innocuous and cost-effective- [76-78].

Applications of green synthesized silver NPs in dentistry

Among metallic NPs, silver NPs (AgNP) are salient in scientific studies for offering biological activity and antimicrobial characteristics against fungi, bacteria, as well as enveloped viruses. There is an association between mechanism of action of AgNPs and the cationic silver release and its oxidative capacity [79]. Also, the shape and size of particles can affect the action mechanism of AgNPs and their synthesis. Thus, it has been proved that silver NP is a promising compound that can be employed in dentistry because some researchers have used the strategy of incorporating antimicrobial substances in dental biomaterial

[80,81]. The effectiveness of silver NPs against many multi-drug-resistant microorganisms has been shown already [82,83]. Nevertheless, the commercial application of silver NPs in dentistry is at early stages, and there are only three products that use AgNPs in their structure and are currently commercially presented: Novaron AG300 (Toagosei Co Ltd., Tokyo, Japan) [84], dental adhesive (NanoCare Gold DNT™) [83,85]., and sealer (GuttaFlow™ Coltène-Whaledent) [86,87].. Hence, the direct use of AgNP in dentistry aims at disinfecting and prophylactic action. According to research findings, the use of AgNPs in dentistry did not provide further clinical and commercial applications or the chemical discriminations of silver NPs and their therapeutic achievement. Thus, in this study, we analyzed the application of silver NPs in technological innovations and dentistry based on their development. Besides, it is attempted to elucidate differences among the physical, chemical, and green synthesis of silver NPs, the NP types utilized in dentistry, and their action mechanisms against fungi and Gram-negative and Gram-positive bacteria. Plants are the most common organisms, which are used in dentistry for the synthesis of silver NPs [88-96]. Strength of this approach is increasing biocompatibility in living organisms that is optimal for the application in the human and veterinary health fields. The biosynthesized silver NP effectiveness is based on the metal core stabilization for biological polymers.

Similar to the chemically synthesized AgNPs, it is possible to use the green AgNPs individually or combined with other dental agents to gain better therapeutic outcomes. Hence, green process developed AgNPs can be a promising approach for producing antimicrobial agents against oral pathogens. Many in vitro research works have been conducted describing the antimicrobial activities of plant-mediated AgNPs against oral pathogens. In AgNPs produced from the leaf extract of Justicia glauca, antimicrobial activity alone and combined with Clarithromycin and Azithromycin has been observed against S. aureus, S. mutans, L. acidophilus, B. subtilis, Micrococcus luteus, E. coli, C. albicans, and P. aeruginosa. Also, these AgNPs have shown effectiveness against different microorganisms that are related to periodontal disease and dental caries, with values of MIC between 25–75 µg/Ml [97]. Another research showed antibacterial activity of biogenic AgNPs generated from plant extracts of Ficus bengalensis (F. bengalensis), Azadirachta indica (A. indica) and Salvadora persica (S. persica) against L. lactis, S. mutans, and L. acidophilus. The S. persica AgNPs and A. indica showed higher effectiveness against the oral pathogens compared to the F. bengalensis AgNPs [98]. It was indicated that Haliclona exigua-AgNPs have the potential of inhibition of biofilms on some microbes engaged in forming oral biofilm, i.e., S. salivarius, S. mitis, and S. oralis [99]. It was shown that AgNPs produced from the aqueous extracts of different rice grain parts (rice husk (RH), rice germ (RG), and rice bran (RB)) have antimicrobial action against E. coli, S. aureus, C. albicans, and S. mutans[100]. The growth of all tested microorganisms was inhibited by AgNPs [100]. According to the findings of a research, the biogenic AgNPs caused improvement of activities in comparison with chemically synthesized AgNPs and CHX. Using extracts of Camellia sinensis (Cs) and Heterotheca inuloides (Hi), the reduction of the chemical AgNPs was made by sodium borohydride ($NaBH_4$), resulting in the production of two green AgNPs [101]. In comparison with Cs-AgNPs, more stable and smaller NPs were produced by Hi. The inhibition of the growth of L. casei and S. mutans occurred better by green AgNPs than 2% CHX, but the smaller Hi-AgNPs showed improved antibacterial activities [102]. Moreover, the greatest antibiofilm and antimicrobial activity against C. albicans and S. mutans was observed in AgNPs produced from extracts of different parts of pomegranate combined with β-calcium glycerophosphate and alone [103]. Also, it is known that Gum acacia-AgNPs show antibacterial action against M. Luteus and E. coli, while no inhibition effects were demonstrated by the G. acacia extracts [104]. Plant extract-mediated AgNPs offer a one-pot approach for in situ synthesis of AgNPs and also provide very stable AgNPs since they function as both stabilizing and reducing agents. It is possible to combine them in various formulations, like toothpastes and mouth rinse for improving their bioactivities [105]. The number of studies examining the cytotoxicity of AgNPs produced by green synthesis for confirming their assumed higher biocompatibility is limited. Despite the high bias in studies that report on AgNPs obtained by green approaches, these NPs can show properties similar to chemically synthesized AgNPs. It has been demonstrated that AgNPs synthesized from Cotyledon orbiculata decrease the possibility of THP-1 differentiated macrophages at concentrations 2.5-20 µg/Ml [106]. AgNPs developed from red pear extracts did not show toxicity to RAW 264.7 cells at concentrations up to 500 µg/mL, whereas the AgNPs produced from green pear extracts caused cell viability reduction with concentrations above 125 µg/mL. These AgNPs presented considerable antibacterial activities at concentrations that lack toxicity to mammalian cells, meaning biocompatibility and safety of these AgNPs for applications at these doses [107]. Many research works unfortunately do not provide proper normal cell controls for comparing the impact of nanomaterials on diseased and normal cells. However, it has been shown that green synthesized AgNPs have superior therapeutic activities. According to research findings, Haliclona exigua-AgNPs have dose-dependent cytotoxicity on the human oral cancer (KB) cell line with half the maximal inhibitory concentration (IC50) of 0.6 mg/mL [99]. Furthermore, AgNPs developed with Amphipterygium adstringens and Glycyrrhiza glabra (G. glabra) extracts caused an inhibition of the bacterial growth of the fungus C. albicans and E. faecalis. Their antiproliferative activities were examined on human epithelial cells, and it was found that AgNPs developed with A. adstringens extract showed higher toxicity to human cells in comparison with the NPs developed with G. glabra extract [108]. Besides, AgNPs synthesized by natural black tea extract showed more cytotoxic activities against ovarian carcinoma in comparison with the colorectal carcinoma cell line [109]. AgNPs have indisputable benefits in dental therapy. However, there are environmental and health concerns related to using nanomaterials. Thus, using risk assessment measures, the safety profile of the AgNPs should be ascertained and ensured before their usage in consumer products, which requires strategies that offer localized AgNP impacts for reduction of bystander cytotoxic effects [110]. Consequently, it is more desirable to consumers to use natural products in dental designs as substitutes to fluoride-based containing dentifrices since it is safer. According to research findings in dentistry, silver NPs are used in various specialties, such as oral microbiology, prosthodontics, preventive dentistry, periodontics, orthodontics, and endodontics. Moreover, there are some studies investigating the capacity of utilizing silver NPs by examining their antimicrobial impacts against the most prevalent oral pathogens. Plant extract-mediated AgNPs both offer a simple one-pot technique for in situ synthesis of AgNPs and synthesizes very stable AgNPs since they function as stabilizing and reducing agents. It is possible to incorporate them in different formulations, like toothpastes and mouth rinse for improving their bioactivities [111]. Also, the green AgNPs is utilized alone or combined with other dental agents to obtain sustainable therapeutic outcomes. It can be concluded that AgNPs synthesized using a green process is a promising approach for producing antimicrobial agents against oral pathogens.

Oral Microbiology

The oral cavity is a microbiome inhabiting above 700 species[112] of protozoa, viruses, and fungi[11]. It is an essential factor in perceiving the etiology of most systemic and oral diseases [112-114], and in most cases, this microbiome is a determining factor of disease and health status. In order to maintain systemic and oral health, the oral microbiota balance is crucial [112]. As indicated by previous studies, the most frequent microorganisms in the healthy oral microbiome are the Proteobacteria, Firmicutes, Actinobacteria phyla, and Fusobacteria. The most prevalent is the genus Streptococcus, and Prevotella, Veillonella, Neisseria, and Haemophilus are in the following ranks [114]. Besides, studies have indicated that AgNP impose antibacterial activity against Staphylococcus aureus [115,120,121,119,122,123], Streptococcus mutans [115-119], Lactobacillus acidophilus, Streptococcus sobrinus, Streptococcus sanguinis [117], Lactobacillus casei, Actinomyces actinomycetemcomitans [117], and Enterococcus faecalis [119,123]. Also, AgNPs avert the growth of S. aureus, E. faecalis, Streptococcus gordonii, Streptococcus mutans biofilms, and Streptococcus mitis [124]. However, it is important to know that these studies investigated the formation of biofilm in monocultures. Dental caries in the oral cavity possesses complex multispecies biofilms. Hence, in vitro data cannot be extrapolated to the clinical application of AgNPs [124]. It has already been revealed that nanoparticles have robust antimicrobial activities against Gram-negative and Gram-positive bacteria in planktonic, biofilm, or agar-grown cultures. Although Gram-positive bacteria have a protective thick external peptidoglycan layer, they are highly susceptible to the antimicrobial activity of silver [124]. Gram-negative bacteria, like Pseudomonas aeruginosa and Escherichia coli, do not show resistance to the silver's antimicrobial action [120-124]. There is an indirect relationship between the antimicrobial effectiveness of nano-silver and the size of silver NPs [125]. Silver NPs that have smaller diameters show better biofilm inhibition results compared to those with larger diameter sizes [126] and are more effective against Streptococcus orallis biofilms [127] and S. mutans [128]. Nevertheless, it has also been indicated that larger AgNPs have considerable antimicrobial activity against various dental plaque microorganisms, which shows appropriate inhibition with bacterial growth even at low concentrations[126]. Antimicrobial activities have been noted in biologically developed AgNP (by the use of onion, tomato, and neem in the synthesis process) with large sizes (26.2-33.3 nm) against S. aureus, potentially for the high concentration of terpenoids and flavonoids [129]. AgNPs were more functional compared to chlorhexidine against Klebsiella pneumoniae, Enterococcus faecalis, S. mutans [125], and C. albicans [130]. According to other studies, pure chlorhexidine shows higher antimicrobial activity against C. albicans and E. faecalis[126-131], and a positive synergistic effect was observed in combination of AgNP with chlorhexidine [131], bio-composites, like antibiotics [132] or calcium glyceride phosphate [133].

Pediatric Dentistry

Dental caries is a dysbiotic disease with a polymicrobial etiology resulting from the imbalance between remineralization and demineralization [134,135]. Dentistry attempts to fight against caries by control of the microbiota and stimulation of the remineralization of emerging lesions on the enamel surface. This is the most frequently employed treatment in primary teeth. Infiltrating carious lesions, silver ions precipitate, which make the enamel harden. Dental surgeons utilize sodium fluoride varnish in the clinical practice for the remineralization of aborning lesions. However, with the addition of 5% of nano-silver to the sodium fluoride varnish, a 77% inhibition is obtained for the progress of caries lesions in residual teeth, without leaving painful ulcers or a metallic taste [136]. Management of silver Nano-fluoride (NSF) is simple, it can be used only once a year, it presents an acceptable cost-benefit ratio, and it is possible to use it for replacement of varnish with sodium fluorine [137] or the traditional silver compound, Silver Diamine Fluoride (SDF). NSF is a bacteriostatic compound since it causes the inhibition of the S. mutans biofilm growth [138]. Moreover, it can paralyze caries activity; thus, it is utilized as an inhibitory treatment that does not stain teeth of children [138,139]. In artificial enamel caries, AgNPs related to a 650 nm Laser [140] and AgNPs in combination with graphene oxide (rGO/Ag) [141] composites reduced the artificial enamel caries' demineralization in a biofilm S. mutans model. Glass ionomer cement (GIC) is broadly applied in pediatric dentistry, and it is popular for its storage capacity and fluoride release. As a result of this release, cement acts as an anti-caries compound, causing inhibition of bacterial enzyme enolase by fluoride. Nevertheless, it requires fluoride recharging occasionally so that its anti-caries impact is maintained. Thus, the functionality of this cement in fighting against oral diseases can be increased by the GIC impregnation with longer-lasting antimicrobial agents. The relationship between AgNP and GIC made a biomaterial with antimicrobial activity against Gram-negative and Gram-positive bacteria [142,143]. With the release of silver ions, the antimicrobial action occurs, causing an oxidative dissolution in the cement matrix, which inhibits dental caries and prevents oral biofilms' development. The union of these materials presents mechanical parameters, such as commercial GIC[143]. According to reports, in testing 12 nm AgNPs in combination with GIC, AgNPs did not show cytotoxicity to odontoblastic lineage cells [144]. Moreover, immobilization of AgNP in Halloysite Nanotubes (HNT/Ag) and its combination with new experimental dental resin composite cause the inhibition of the growth of S. mutans without any related cytotoxicity [145]. In previous studies, AgNP has been included in a resin matrix based on bisphenol A-glycidyl methacrylate/ triethylene glycol dimethacrylate (BISGMA/TEGDMA) that is employed in repairs of permanent and deciduous dentitions through chitosan polymers. Antimicrobial action against S. mitis was discovered, which represents a reduction of antimicrobial activity by the coating of restorative materials with the polymer [146]. However, it has been indicated that there is an incomplete nanocomposite polymerization (resin + AgNP) with increased release of unbound monomers [147]. In the literature, it is not clearly stated whether it is possible to combine AgNPs with polymer resins in restorative dentistry [148,149].

The material marginal infiltration was not reduced by the AgNP incorporation with composite resins [150]. The polymerization type affected the final mechanical properties of these nanocomposites [151]. The application of photopolymerization for forming resins used with silver NPs did not enhance the mechanical characteristics in comparison with commercial resins [152].

Cohesive failures and surface wetting were improved by dentin adhesives related to AgNPs [153]. It was noticed that there was antimicrobial activity when testing AgNP and self-etching adhesives against S. mutans, and the conversion of adhesive into the resin was not compromise [154] . The incorporation of AgNP increased durability of the antibacterial activity. It can be used for instant antibacterial needs [155]. Greater shear strength was observed in two-step adhesive systems related to AgNP compared to self-etchers/AgNP [156]. AgNP powder provided better outcomes compared to the alcoholic AgNP solution in terms of the conversion degree of the self-etching adhesive and antimicrobial activity [154]. As a result of incorporation of AgNP in antiseptics, biocompatible commercial products (Nanocare Gold) have been obtained without cytotoxicity to stem cells from dental pulp [142].

Orthodontics

The cleaning process is slowed down due to the existence of fixed orthodontic appliances on surface of teeth, which results in the accumulation of dental biofilm [157]. The most prevalent consequence in individuals using fixed orthodontic appliances is incipient caries lesions, called white spots, which is particularly evident when oral hygiene is poor [158] . After applying orthodontic appliances, the Lactobacilli spp. And Streptococcus mutans increase in dentition, saliva, and plaque formation [159]. For avoiding this condition, AgNP has been used for treating elastomeric modules, titanium micro-implants, orthodontic wire, and brackets [117,126,160].

AgNP treatment caused demineralization reduction in individuals under orthodontic therapy, and antibacterial activities were observed against L. casei, E. coli, S. aureus, S. mutans[160]. AgNP presented non-stick biological characteristics in brackets and wires[126] against S. mutans [120,126,161]. It should be mentioned that only one research examined varying sizes of silver NPs, and better outcomes were obtained with smaller-sized particles [126]. As shown by the reduced emergence of dental caries on smooth surfaces following impregnation of AgNPs, the antibacterial action of silver NPs has contact inhibition features and not only with ion release [161]. Besides, NPs have been used in acrylic resins, base plates of orthodontic appliances, inhibiting the formation of biofilm and planktonic growth [116]. Antimicrobial activity was noted in titanium micro-implants treated with 21% AgNP and biopolymer [117]. It was also observed in AgNP and GIC composites employed in orthodontic cementation, which could decline the metabolic activity of the biofilm and the production of the bacterial acid [158].

Endodontics

Apical periodontitis is essentially caused by necrotic or inflamed pulp that is a colonization complication by microorganisms, which can result in bone infection [162]. Despite polymicrobial etiology, there is Enterococcus faecalis, an anaerobic, facultative Gram-positive bacterium, in infected root canals, which causes persistent infections treatment of which is problematic. E. faecalis biofilm is disrupted by combining AgNP with composites through releasing silver ions [163]. Besides, when AgNPs were employed as final endodontic irrigators, their antimicrobial effect was indicated, which is like the 2.5% sodium hypochlorite treatment [164].

Mineral trioxide aggregate (MTA) and calcium-based cement associated with AgNP showed antimicrobial action against Actinomyces spp., Streptococcus mutans, Escherichia coli, C. albicans isolates, and E. faecalis. Silver particles are able to reduce the microorganisms' attachment to the surface of the tooth and improve the antibacterial characteristics of endodontic sealers [165]. Also, such particles caused an increase in the MTA radiopacity [166].

Periodontics

In the analysis of the AgNP use in dentistry, the most important point is to determine the ideal concentration toxic to microorganisms and not cytotoxic to the cells of the patient so that it is ensured that healthy tissues are not changed. Silver NPs are toxic against microorganisms that generate dental caries and may be active for oral cavity tissues and other cells. Hence, the AgNP action on human oral keratinocytes [167] and human gingival fibroblasts [168,169] has been shown in some studies.

As a result of the relationship of AgNPs with sodium fluoride or fluorine[168], oxidative stress increases in gingival fibroblasts, which results in inflammation of tissues, leading to apoptosis and compromising cell viability [170], while 2 nm AgNPs at a concentration of 1.5 ug/mL did not show any cytotoxic activity.

Biocompatibility can be improved by the strategy of capping silver NPs through forming surface functionalization[168]. The cytotoxic impacts against human gingival fibroblasts were decreased at nontoxic concentrations (<50 µg/mL) by 10 nm NPs capped with polyethylene glycol or lipoic acid toxic concentrations, and considerable antimicrobial potential[168] and inhibition of S. mutans strain biofilms and methicillin-resistant S. epidermidis were noted. Results demonstrated a relationship between the AgNP cytotoxicity in human oral keratinocytes and inflammatory processes and lysosomal damage, and due to activation of NLRP3 inflammasomes by high AgNP concentrations, the number of acidic organelles is reduced, resulting in cathepsin B expression [171].

Prosthodontics

This field is classified into two areas: dental prosthesis and dental implantology. Prosthodontics comprises planning for treatment, diagnosis, rehabilitation, and preservation of the oral appearance and function, health, and comfort in clinical conditions related to deficient or missing teeth and/or maxillofacial and oral tissues by the use of biocompatible substitutes [172].

Dental Implantology

Implant failure, known as peri-implantitis, mainly occurs due to bacterial biofilm formation on the dental implants' surfaces. The lengthy AgNP deposition has a harmful interference in the surface properties, which increases the hydrophobicity and roughness, and the likelihood of adherence of oral bacteria is higher in these conditions. The 0.1 ppm concentration was toxic to human osteoblasts [173]. It has been suggested that the modification of surface nanotopography influences bacterial adherence to implants [174].

The lactate production by microorganisms and biofilm adhesion was reduced by titanium discs treated with AgNP-based composites, though some cracks were presented [174]. With coating titanium discs with AgNP and hydroxyapatite, they present activities against E. coli [175]. By applying AgNP suspension on the implants' surface with hexagonal links, a reduction was observed in C. albicans contamination [176].

With the treatment of hydrogentitanate nanotubes with AgNP, it was found that there is a long-lasting antibacterial effect against E. coli since it presented a long-term Ag+ release [177]. With treatment of titanium with varying concentrations of polyoxoxamine (PDA) and silver [178], antibacterial activity against

P. gingivalis and S. mutans was found. When AgNPs were directly developed on the titanium plate with no toxic effect on human dental pulp stem cells, they presented antibacterial effect against S. mutans [179]. Using Silver plasma conditions, titanium implants with hierarchical nano/ microstructures show antibacterial activity against and Gram-negative Fusobacterium nucleatum and Gram-positive S. aureus [180] . Besides, it was indicated that treatment of implants with Silver Plasma provides higher osteointegration compared to acid-treated implants [181]. As a result of the association of AgNPs with NRL (Natural Rubber Membrane), cytotoxicity reduced, presenting 98% cell viability [182]. Due to the guided tissue regeneration of membrane impregnated with silver NPs, the tensile strength increased and the biomaterial's fiber diameter was minimized [183].

Dental Prosthesis

There is the problem of C. albicans infections in the PMMA resin-based prosthetic devices [184-186], affecting their useful life. Protocols have been presented for periodic chemical cleaning of prostheses for eliminating these infections. Nevertheless, due to treatment repetition, the prosthesis surface is damaged and the longevity of prosthetic devices and implants is compromised [187-189]. Prosthetic devices and molds in dentistry were produced by using compounds based on PMMA, silicones, BISGMA/TEDGMA, tissue conditioners, porcelain, and alginates, and with adding AgNPs, antimicrobial effects enhance according to the concentration of NPs [190]. The mechanical characteristics of the impression material did not alter with the addition of AgNPs to alginates [191], while the setting time was reduced and the solubilization of Portland cement was increased [192]. Research findings indicate that the appropriate strategy for improvement of the performance of PMMA matrices is structural modifications at the nanoscale or by combining with composites. The mix of 1% silver graphene has been demonstrated to improve the mechanical characteristics of PMMA [193], increasing their viscoelastic properties [194]. Antibacterial properties were observed as a result of the combination of AgNPs and titanium dioxide, and the material mechanical properties did not improve [195]. Additionally, it was demonstrated that the antibiofilm activity was improved by the association of AgNPs with quaternary ammonium dimethacrylate (QADM) [196]. The incorporation of AgNPs into ethylene-vinyl acetate copolymer masterbatch inhibited the growth of Streptococcus sobrinus, Porphyromonas gingivalis, and E. coli without any damage to the mouthguard [197]. With the incorporation of this material with AgNPs, it resulted in increased fracture resistance, the useful life of porcelains, and fatigue parameter [198,199]. In a multifunctional biogenic composite, with mixing NPs with PMMA, a reduction was observed in 2-methacryloyloxyethyl phosphorylcholine (MPC), dimethylaminohexadecyl methacrylate root dentin demineralization, and amorphous calcium phosphate [200] . The AgNPs change colors in prosthetic devices [201,202]. Changes in color were due to the AgNP plasmatic impact via electronic propagation as an electromagnetic wave in the visible light spectrum [203,204].

Conclusion

There is a global growth in researches and technological development on AgNP in the dentistry area, indicating the increase in research on this technology, which has already proven the antimicrobial activity of AgNPs. Thus, AgNPs acts as an antimicrobial agent for use in the control of bacteria, caries activity, tissue inflammation, and bone loss, when at concentrations presenting low cytotoxicity to the patient's cells.

Declaration of Competing Interest

The authors declare no conflicts of interests.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this review.

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