

Silver nanoparticles in medicine and technology: Synthesis, functionality and future prospects

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Abstract

Nanomaterials, particularly nanoparticles (NPs), have emerged as forefront materials of the 21st century due to their unique properties and potential applications. Silver nanoparticles (AgNPs) are among the most attractive inorganic nanomaterials, widely used due to their significant antibacterial properties, broad-spectrum activity, and potential applications across various fields, including health, food storage, textiles, and environmental solutions. AgNPs exhibit a large surface-area-to-volume ratio, enabling enhanced interaction with bacterial cells, making them effective in medical and industrial applications. Despite concerns over their toxicity, AgNP-based products have been approved by multiple regulatory bodies.

Nanoparticle synthesis methods are generally divided into physical, chemical, and biological approaches. Although physical and chemical methods are efficient, they involve toxic chemicals and energy-intensive processes. Biosynthesis, particularly plant-based, offers an eco-friendly alternative, reducing the environmental and health risks associated with chemical agents. The review also explores the therapeutic potential of AgNPs in drug delivery systems, especially in topical formulations like nanoemulsions, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). These nanocarriers enhance drug stability, skin penetration, and controlled release, making them ideal for dermal and transdermal delivery.

Moreover, the use of AgNPs in dentistry is highlighted for their bactericidal properties, which help prevent infections and implant failure, with the potential for enhancing therapeutic outcomes without common drawbacks like tooth staining. Overall, AgNPs exhibit promising applications in biomedical, pharmaceutical, and dental fields, and their novel functionalities continue to advance the development of nanotechnology-driven solutions.

Keywords: silver nanoparticles (AgNPs); nanoparticles (NPs); Topical drug delivery system (TDDS); small unilamellar vesicles (SUV); multi-lamellar vesicles (MLV); silverdiamine fluoride (SDF); localized surface plasmon resonance (LSPR); skin discoloration (argyria); vascular endothelial growth factor (VEGF).

1. Introduction

In recent decades, nanomaterials (NPs) have emerged as one of the most innovative materials. They have been dubbed the "material of the 21st century" due to their distinct designs and combinations of properties that set them apart from traditional materials [1]. The term "nano" denotes a billionth of a meter, or 10^{-9} [2]. Two general categories for nanoparticles are (i) inorganic and (ii) organic. Organic nanoparticles include carbon nanoparticles (like fullerenes, quantum dots, and carbon nano tubes), whereas inorganic nanoparticles include semi-conductor nanoparticles (like Zn O, ZnS, and Cd's), metallic nanoparticles (like Au, Ag, Cu, and Al), and magnetic nanoparticles (like Co, Fe, and Ni). Nanoparticles of gold and silver (noble metals) offer exceptional properties and practical flexibility [3].

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Because of its broad range of activity against pathogens like bacteria, viruses, fungus, and protozoa, silver has also been utilized extensively as a universal medicinal agent. Since antibiotics were developed and Alexander Fleming discovered penicillin in 1928, the use of silver was restricted because of the exorbitant expense of producing it. Antibiotic treatment is currently widely used. Overuse of antibiotics, which is frequently insufficient to treat dental conditions, leads to the emergence of resistant bacterial strains such as *Bacillus amyloquelificans* [4, 5].

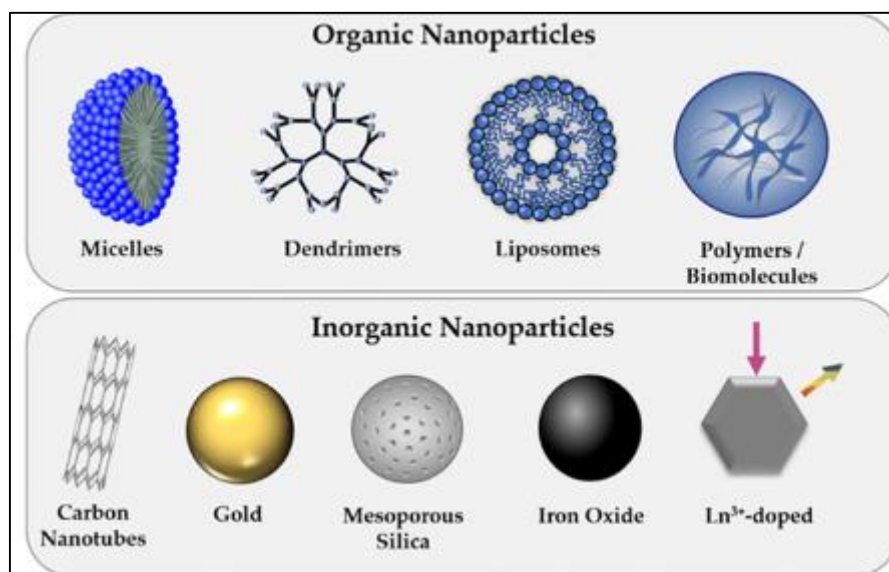


Figure 1 Overview of commonly used nanoparticle (NP) types, classified as organic, inorganic, or composite structure

Silver nanocrystals, which are primarily hydrosols, are among the most appealing inorganic materials due to their many uses in photography [6]. AgNPs are a type of zero-dimensional materials that range in size from 1 nm to 100 nm and have unique morphologies [7]. The availability of increased surface area is primarily responsible for the high efficiency of silver nanoparticles.

Compared to micro-sized silver ions, the area to volume ratio for interactions facilitates the penetration and disruption of nanoparticles into the bacterial cells.[8]

AgNPs have found widespread use as anti-bacterial agents in a variety of environmental applications, food storage, textile coatings, and the health sector. It is significant to remember that there is still uncertainty regarding the toxicity of silver, even after decades of use. Numerous recognized organizations, such as the US FDA, US EPA, SIAA of Japan, Korea's Testing and Research Institute for Chemical Industry, and FITI Testing and Research Institute, have authorized products created with AgNPs.[9]

Drug items used for local action or systemic effects are the two types that are dermally given through the skin. Applying something on or near the skin's surface can have a localized effect on the stratum corneum or alter the function of the epidermis or dermis. Local actions include gels, creams, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, and solutions. Yetisen and associates. [10]

2. Synthesis of nanoparticles

2.1. Synthesis of AgNPs Using Physical And Chemical Methods-

Silver nanoparticles are generally synthesized via physical, chemical, and biological techniques. But many of these techniques involve hazardous, farmable, and difficult-to-remove chemicals that endanger both people and the environment [10,11]. One approach that appears to be promising for producing nanoparticles quickly, easily, safely, economically, and environmentally is biosynthesis [12,13, 14].

The benefits of physical approaches include speed, the use of radiation as a reducing agent, and the absence of toxic chemicals; however, the drawbacks include high energy consumption and low yield, solvent contamination, and non-uniform distribution [15–19]. Silver nanoparticles are prepared chemically using either water or organic solvents [20, 21]. AgNP Synthesis Metal precursors, reducing agents, and stabilizing or capping agents are needed in the solution. Reducing agents that are frequently utilized include sodium citrate, alcohol, borohydride, ascorbic acid, and hydrazine compounds. The Prasines and Sotiriou approach.[22]

Various biomedical sectors have employed a variety of silver nanostructures with unique features [23]. A wide range of products, including electronic devices, paints, coatings, soaps, detergents, bandages, etc., have used silver nanoparticles of various sizes and forms [24].

Therefore, it is essential to consider certain physical, optical, and chemical characteristics of silver nanoparticles in order to maximize their utility in these applications. Surface property, size distribution, apparent morphology, particle composition, dissolution rate (i.e., reactivity in solution and efficiency of ion release), and types of reducing and capping agents used are all significant details of the materials to take into account during their synthesis. The two primary ways for synthesizing metal nanoparticles (NPs) are top-down and bottom-up, as seen in Figure 2. The top-down method excludes bulk materials. The bottom-up approach creates nano-sized materials by assembling individual atoms and molecules into larger nanostructures in order to create the necessary nanostructures [25].

Nanotechnology uses the findings of nanoscience to create novel materials and useful infrastructure. Currently, one of the primary areas of nanoscience that is expanding is nanochemistry [26].

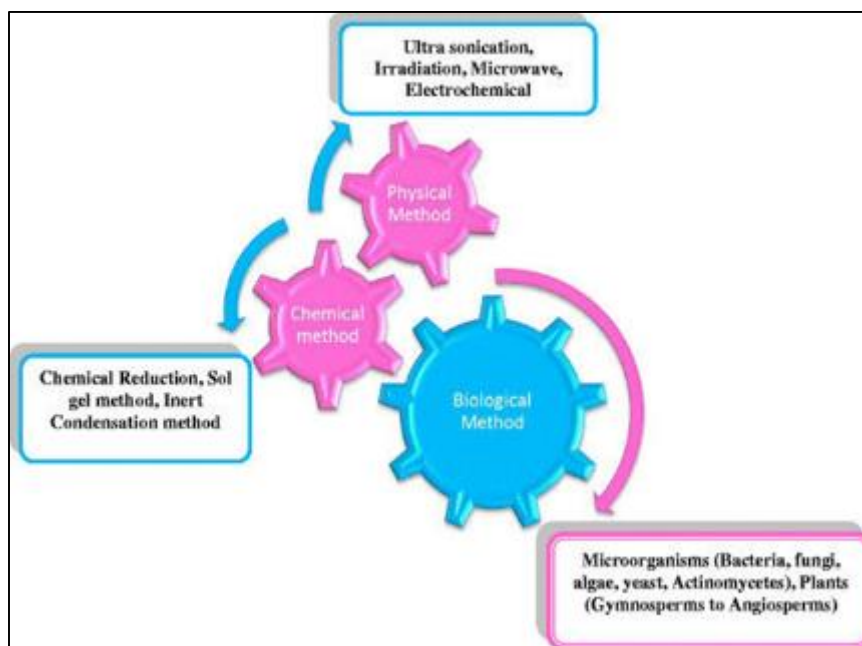


Figure 2 Methodes involved in nanoparticles synthesis

2.2. Synthesis Of Agnp Using Biological Methode

A great deal of interest has been shown in the biosynthesis of nanoparticles, particularly silver nanomaterials, from organic or plant extracts due to their many uses and diverse array of bioactive reducing metabolites. It is well recognized that plants are a very desirable source for creating nanoparticles. Plants are more resistant to metal toxicity than bacteria and algae, making them a more environmentally friendly option for producing silver nanoparticles [27, 28].

Because they are the source of photosynthesis and have more available H_p ions to lessen the production of silver nitrate within the silver nanoparticles, green leaves are utilized and preferred in this instance over other plants when producing silver nanoparticles. Ephedra intermedia stem extract has been effectively used to develop green synthesis of silver nanoparticles (Ag NPs). To find the ideal circumstances, the impact of reaction temperature, amount of stem extract, and concentration of silver precursor on the bio-reduction reaction was assessed. It was discovered that the natural carbohydrates found in Ephedra intermedia functioned as efficient reducing and capping agents during the production of AgNPs [29].

Therefore, there are certain drawbacks to creating Ag NPs chemically, including the fact that they are hazardous to human health and the environment and, more importantly, that they damage many normal cells, which could lead to major issues. Silver, however, was discovered to have distinct impacts on a range of cultivated cells.

Only silver exhibited notable cytotoxicity as compared to other metals; nevertheless, lowering aberrant cellular activity (characterized by asymmetrical forms and morphology) and raising the dosage of silver can cause cellular shrinkage. When synthesizing Ag NPs, biological agents are preferable over chemical ones because they are more economical, environmentally friendly, and use fewer hazardous reagents and solvents, which can reduce toxicity and increase material energy efficiency [30]. Because harmful bacteria have the potential to infect the nanoparticles utilized in medical areas, using plant extract for nanoparticle synthesis has been shown to have more advantages than microbial procedures [31].

Here, the most discussed nanomaterials in terms of exposure analysis and hazard assessment are listed in A selection of representative nanomaterials are presented based on their primary applications and intrinsic physicochemical characteristics through a classification of nanomaterial compositions. Although they are frequently utilized as comparatively "inert" nanoparticles for comparison purposes in the context of environmental nanotoxicology, gold nanoparticles (Au NPs), which are recognized as one of the most significant materials with potential for usage in biomedical disciplines, are not included in [32].

3. Novelty of silver nanoparticles

Nanotechnology is an emerging field of science that mainly deals with nanomaterials to overcome size limitations and change the world perspective on science. It has revolutionized agriculture sectors and played essential roles in various fields like agricultural biotechnology, food security, and crop production. Nanoparticles distinct physicochemical features are extremely helpful in inducing plant metabolism.

However, their interactions with plants have not been clarified and understood in detail. Several contradicting reports of nanoparticles regarding accumulation, translocation, absorption, biotransformation, and toxicity were reported in diverse plant species. AgNPs are one of the most significant nanomaterials whose impacts are still under Figure 3 Nanoparticles as novel topical drug delivery system (TDDS) used to improve skin penetration, dermal and transdermal delivery investigation [33,34].

The use of metal nanoparticles is not limited to molecular detection; recently, AgNPs have been used as delivery vehicles for therapeutic agents, including antisense oligonucleotides and other small molecules. Noble metal nanoparticles have specific high developed photophysical properties which contribute to their potential as photoactivated drug delivery vectors. AgNPs have been used extensively as biological sensors which take advantage of plasmon resonance (PR) to enhance detection of specific targets. Noble metal nanoparticles based sensors benefit from the extreme sensitivity of localized surface plasmon resonance (LSPR) spectra to environmental changes.

Modifiable in size and shape, high-density surface ligand attachment, improved stability of surface-bound nucleic acids, transmembrane delivery without harsh transfection agents, defense against therapeutic degradation, and potential for better timed/controlled intracellular release are just a few of the many benefits that small metal nanoparticles (NPs) offer as drug carriers. AgNPs' photophysical characteristics have the potential to advance drug delivery by facilitating targeted administration, spatiotemporally regulated (photo)release, and imaging-based delivery confirmation.[35]

Colloidal systems with an average diameter of less than 500 nanometers are referred to as nanocarriers.[36] Dermal and transdermal drug delivery has been the main focus of research on novel nanocarriers, including microemulsion, liposome, and nanoparticulate carriers. As topical drug delivery systems, nanoparticles offer numerous benefits, including increased drug deposition in the target area, improved drug loading stability in the form of greater physicochemical stability, and sustained and regulated drug administration from nanoparticulate systems. Lipid-based nanoparticles, including liposomes, niosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), were extensively studied as topical drug delivery methods in the literature. To accomplish cutaneous and transdermal drug administration, other materials such as polymeric nanoparticles, metal nanoparticles, nanocrystals, and nanospheres, as seen in Figure 3, were also explored.[37]

Hair follicles are a viable route for augmenting dermal and transdermal administration penetration into the skin. Regardless of the kind of nanoparticles, the most crucial factor that could influence the depth of follicular penetration is their average diameter.[38] Targeting individual hair follicles specifically may be a fantastic way to treat hirsutism, androgenetic alopecia, and acne vulgaris. The benefits of trans-follicular drug delivery include tissue targeting, deep

penetration into epidermal layers, long-term drug deposition and storage, and increased cutaneous bioavailability. Nevertheless, there are a number of difficulties with transdermal administration via hair follicles.[39]

such as inadequate transdermal delivery system characteristics (adhesion, permeability, storage, shelf life, etc.), biological factors (site of application and variability in skin permeation), and poor physicochemical properties of active pharmaceuticals (solubility, pharmacokinetics, metabolism, compatibility, etc.) that need to be addressed.[40]

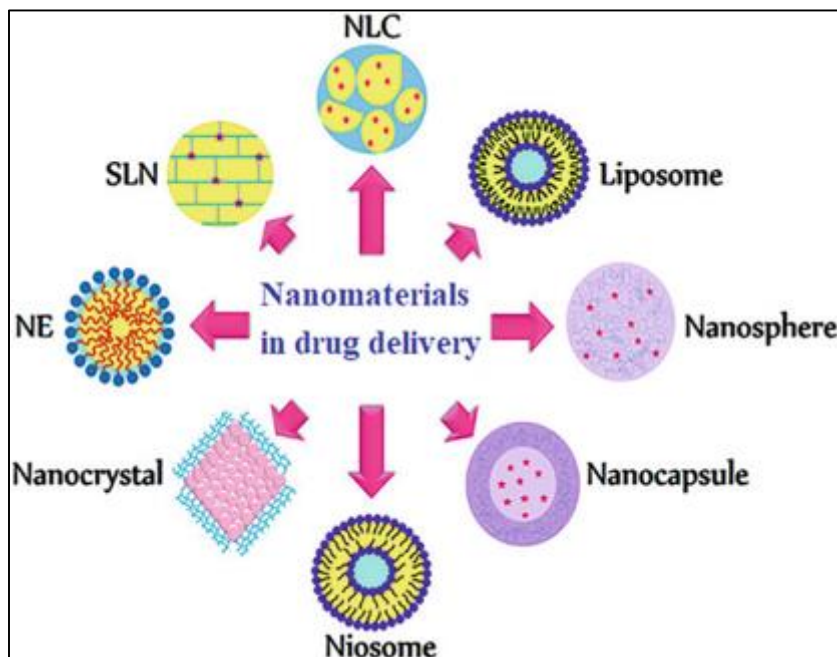


Figure 3 Nanoparticles as novel topical drug delivery system (TDDS) used to improve skin penetration, dermal and transdermal delivery

3.1. Nanoemulsions (NEs)

With their translucent nature, smooth skin feel, regulated and prolonged drug release, simplicity of self-administration, and lack of gastrointestinal side effects, NEs are also promising nanocarriers for transdermal drug delivery to systemic circulation.[41]

Through a variety of methods, including an increase in the drug's solubility in the carrier, carrier uptake into the stratum corneum and fluidization, and changes and dissolution of the stratum corneum lipids, NE containing penetration enhancers may boost skin penetration. Hydrophilic and lipophilic drug distribution can be enhanced transdermally by NEs containing oils and surfactants in their formulations.[42]

3.2. Solid Lipid Nanoparticles (SLNs)

The first class of lipid-based nanocarriers made of solid lipids and emulsifiers are called solid lipid nanoparticles (SLNs). They are made from lipids that, at normal temperature, are totally solid. [43] Topical drug delivery systems, or SLNs, possess the ability to be both adhesive and occlusive. This allows them to create a uniform and homogenous layer on the stratum corneum, prolong their residence time, and improve skin penetration by interacting with the skin's layers and altering their barrier properties. In comparison to free medications for the treatment of psoriasis, a reported study shown that SLNs could greatly improve the amount and depth of cyclosporine A and calcipotriol skin penetration.[44]

3.3. Nanostructured Lipid Carriers (NLCs)

The second generation of lipid nanoparticles, known as NLCs, are made up of a combination of liquid and solid lipids. These nanoparticles show promise as delivery vehicles for cosmetics and pharmaceuticals, including follicular, transdermal, and dermal applications. Drug protection, regulated drug release, increased drug bioavailability, and improved skin penetration and deposition are just a few benefits of using these kinds of nanocarriers. By preventing trans-epidermal water loss and forming a film at the stratum corneum's surface, NLCs can help improve skin moisture. For the treatment of androgenic skin conditions such as acne, hirsutism, and alopecia, follicular distribution of

active medicines is another exciting use for lipid nanoparticles, particularly NLCs. The size of the nanoparticles is the primary determinant affecting the quantity and depth of follicular delivery [45].

3.4. Liposomes

A vesicle known as a liposome is made up of one or more lipid bilayers with an embedded aqueous phase. Liposomes typically contain cholesterol and phospholipids. For topical medication administration, liposomes vesicular nanocarriers offer a number of benefits, including regulated release of the drug, targeted drug deposition in skin layers, decreased systemic absorption, and fewer adverse effects. Lower serum concentrations and drug excretion in urine were used as evidence of localized skin deposition of active medicines loaded liposomes.[46]

Particle size, fluidity, lamellarity, occlusive qualities, and liposome types and compositions all have a significant impact on the drug-loaded liposome's deposition efficiency.

Smaller liposomes have been shown to penetrate deeper into the skin layers, and small unilamellar vesicles (SUV) have been shown to increase skin penetration more than multi-lamellar vesicles (MLV). These findings highlight the importance of liposome particle size in skin penetration.[47]

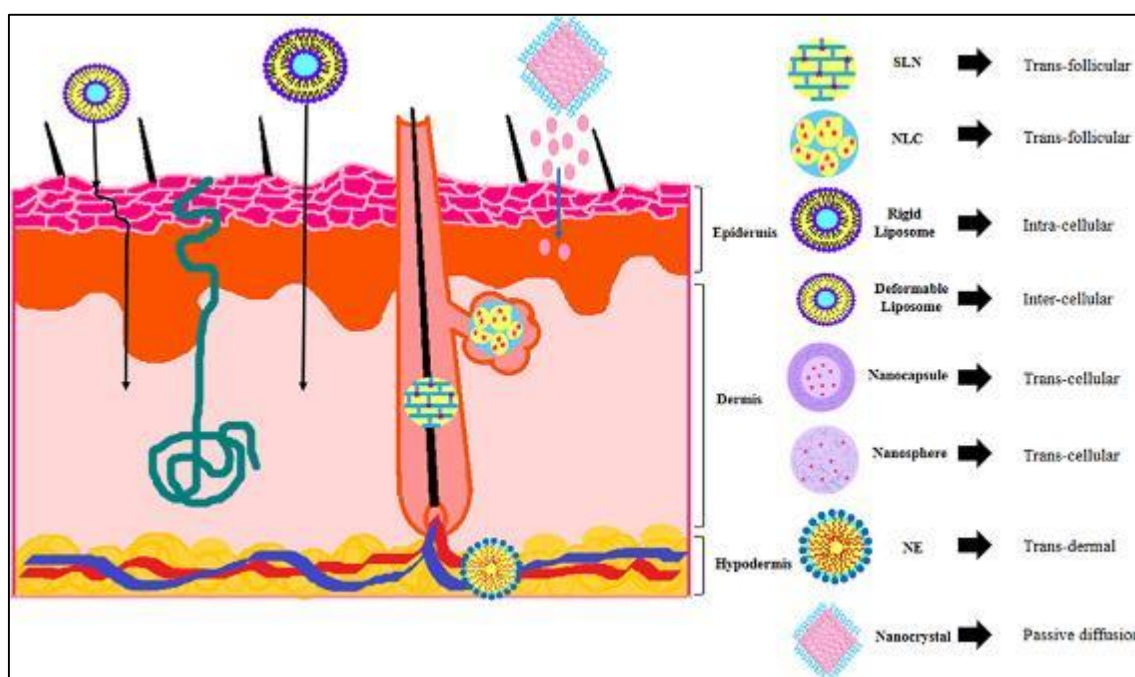


Figure 4 A schematic view of different nanocarriers mechanisms in skin permeation enhancement and targeted delivery to skin organelles

3.5. Niosomes

The other kind of vesicular drug delivery system has a spheroidal form and can be one or more layers deep. These are called niosomes. They are created when molecules that are amphiphilic come together. Niosomes are vesicular drug delivery systems made of nonionic surfactant that are presented as an alternative to traditional liposomes.[48] Niosomes are useful as nanocarriers for proteins, peptides, and chemical medications. One crucial factor impacting niosome-mediated transdermal drug distribution is the fluidity of the vesicular membrane. Essential oils, particularly terpenes, play a significant role in niosome compositions because they can improve penetration by upsetting the structure of the stratum corneum. Additionally, essential oils may improve the niosomes' flexibility and facilitate vesicle fluidization, both of which may improve transdermal medication delivery.[49]

3.6. Nanocrystals

Particulate systems called nanocrystals are made completely of medication. The size of their particles varies from 1 to 1000 nm. Although the most significant disadvantage is the requirement for frequent dose administration, nanocrystals are appropriate drug delivery systems for essentially insoluble active pharmaceuticals, medications with limited skin penetration, and less bioactive compounds. According to a study, dexamethasone-loaded ethyl cellulose nanocarriers

and regular dexamethasone cream did not improve skin penetration as much as dexamethasone nanocrystals. Furthermore, compared to conventional or ethyl cellulose nanocarrier formulations, where the majority of the drug remained in the epidermis, the results showed that in the nanocrystal formulation, the majority of the medication was accumulated in the dermis layer.

Additionally, the use of nanocrystal formulation resulted in faster skin penetration.[50]

4. Mode of action and applications

4.1. Dental application

In order to prevent the pathogenic contamination of dental implants, proper tooth-brushing techniques, prophylactic antibiotics, and antimicrobial mouthwashes are specifically recommended. A major goal in dentistry is to provide the proper protection of the oral cavity, which represents a pathogenic-susceptible gateway for the entire body. Biofilms developed on dental implant surfaces may additionally cause inflammatory lesions on the peri-implant mucosa, thus increasing the risk of implant failure.

Adding silver-based nanostructures to or altering common dental materials is an appealing tactic that dentists around the world are using to give them extra bactericidal benefits. While silver, in the form of nano silver diamine fluoride (SDF), has beneficial effects in caries prophylaxis, there are drawbacks to using this specific molecule, with tooth discoloration being one of the most obvious. The use of nano silver could stop black staining in teeth, which typically happens after app-based sensors take advantage of the extremely sensitive localized surface plasmon resonance (LSPR) spectra to environmental changes. By significantly increasing the contact surface, AgNPs' antimicrobial properties would be enhanced. Metal nanoparticle application is not an attractive strategy embraced by worldwide practitioners in order to provide additional bactericidal effects to general-use dental materials is to modify or embed them with silver-based nanostructures. Though silver has favorable effects in caries prophylaxis in the form of nano silver diamine fluoride (SDF), the use of this particular compound has some disadvantages, one of the most noticeable effects being represented by tooth staining. By reducing the size of AgNPs, the contact surface will be considerably increased; in this way, the antimicrobial effects of silver would be improved, and the use of nano silver could prevent black staining in teeth, which usually occurs after the app-based sensors benefit from the extreme sensitivity of localized surface plasmon resonance (LSPR) spectra to environmental changes. Application of metal nanoparticles is not limited to molecular detection.

Recently, AgNPs have been harnessed as delivery vehicles for therapeutic agents, including antisense oligonucleotides and other small molecules. Small metal NPs offer many advantages as drug carriers, including adjustable size and shape, enhanced stability of surface-bound nucleic acids, high-density surface ligand attachment, transmembrane delivery without harsh transfection agents, protection of the attached therapeutic from degradation, and potential for improved timed/controlled intracellular release. The photophysical properties of AgNPs may potentially bring these to the forefront of drug delivery, enabling targeted delivery, spatiotemporally controlled (photo-)release, and delivery confirmation via imaging location of SDF [51]

4.2. Antibiotic application

An alarming phenomenon of current healthcare practice is the occurrence of many drug-resistant microorganisms, which leads to ineffective conventional monotherapy. Bacterial infections and their related complications represent a major and frequent cause of death.

With the aim to overcome the limitations that occurred due to drug-resistant pathogens, worldwide research focused on the investigation of antibacterial resistance mechanisms, as well as on the development and optimization of unconventional and effective antibacterial strategies. Silver-based compounds have been used as antimicrobial agents for thousands of years, proving the ability to go through biological membranes and to exhibit local or systemic effects, thus being used for different treatments, including dental and digestive pathologies, wounds and burns healing.

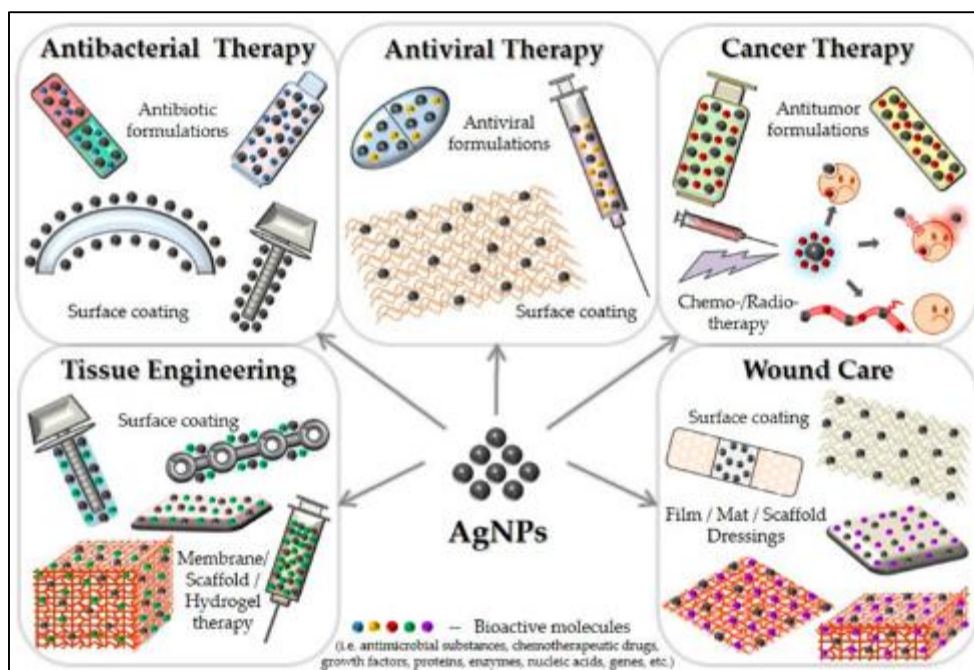


Figure 5 Applications of silver nanoparticles (AgNPs)

Despite their remarkable therapeutic properties, the weakness of such compounds is related to their toxicity on human cells, which occur at higher concentrations. In addition, if prolonged treatment with silver-based compounds is applied, their accumulation in the organism may lead to vital organs' impairment and skin discoloration (argyria). Therefore, to overcome cytotoxicity, products containing silver compounds and nanoparticles require very low metallic concentrations and suitable delivery systems. Ag NPs exert their activity through several antibacterial mechanisms which reduce the possibility of resistance development to Ag NPs. Ag is dissolved in aqueous solution forming Ag⁺ ions which act as antimicrobial agent (Fig 5). One of the antibacterial mechanisms of Ag⁺ ions is due to their interaction with sulfur phosphorus groups in the structure of proteins of the cell wall and plasma membrane of bacteria which lead to dysfunction of these proteins thereby threatening organisms' life [52].

On the other hand, silver ions bind to negatively charged parts of the membrane thus creating holes in the membrane, causing cytoplasmic contents flowing out of the cell. Therefore, the proton gradient dissipates across the membrane and finally causes cell death [53]. Thereafter, the existence of silver ions inside the cell can disturb the function of the electron transport chain of the bacteria. Silver Ag⁺ ions also bind to DNA and RNA of the bacteria and inhibit cell division [54].

Chemically synthesized spherical AgNPs showed more effective killing bacteria ability than rod-shaped counterparts when used against both Gram-negative and Gram-positive pathogens. It was evidenced that the antibacterial activity of nanosilver is strongly related to their microstructure, namely the presence of (1 1 1) crystallographic plane [55].

4.3. Antiviral application

The intrinsic antiviral mechanism of silver nanoparticles is not completely known and understood, the studies requiring more complex structural, molecular and immunological research than in the case of antibacterial properties. In a similar way with their antibacterial activity, the antiviral effects induced by AgNPs rely on the specific affinity for essential biomolecules (viral proteins and glycoproteins, enzymes, lipids, nucleic acids) and Ag⁺-mediated biostatic events, such as obstruction of cellular attachment and invasion, the arrest of intracellular viral replication or propagation, hinder of extracellular virions production.

Nano silver-based formulations proved efficient therapeutic effects against several pathologies caused by clinically relevant viruses, such as severe acute respiratory syndrome coronavirus, human papilloma virus (HPV), rotavirus and other enteric viruses. It is worth mentioning that new and effective platforms containing AgNPs were evaluated for their biocidal activity against viral vectors, generally mosquito-borne pathogens including Zika virus, Dengue virus, West Nile virus and Chikungunya virus [56].

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4.4. Cancer Therapy

Many studies have shown that silver nanoparticles have made their way into therapeutic applications in cancer as anti-cancer agents. Several in vitro studies have indicated that silver nanoparticles can enter cells by endocytosis and their localization inside the cell can be determined as the perinuclear space of cytoplasm and endo-lysosomal compartment. Besides, silver nanoparticles can enter the mitochondria and produce reactive oxygen species (ROS) by affecting the respiration of cells. In summary, the mechanisms of AgNPs as toxic can lead to DNA damage, oxidative stress, induction of apoptosis, and mitochondrial damage to cancer cells. The mechanism of action of silver nanoparticles on cancer cells is schematized in (figure .6). Furthermore, there are studies that AgNPs affect the function of the vascular endothelial growth factor (VEGF). It is also known as vascular permeability factor and plays a major role in the angiogenesis within tumors. These results support AgNPs have anti-cancer properties that can be used as an alternative for cancer therapy and angiogenesis inhibitor therapy.

Theranostic applications of green-synthesized nanoparticles were investigated for biologically compatible and potential approaches in biomedical field (antimicrobial, anti-inflammatory, antinociceptive, anticancer and enzyme inhibition activities).

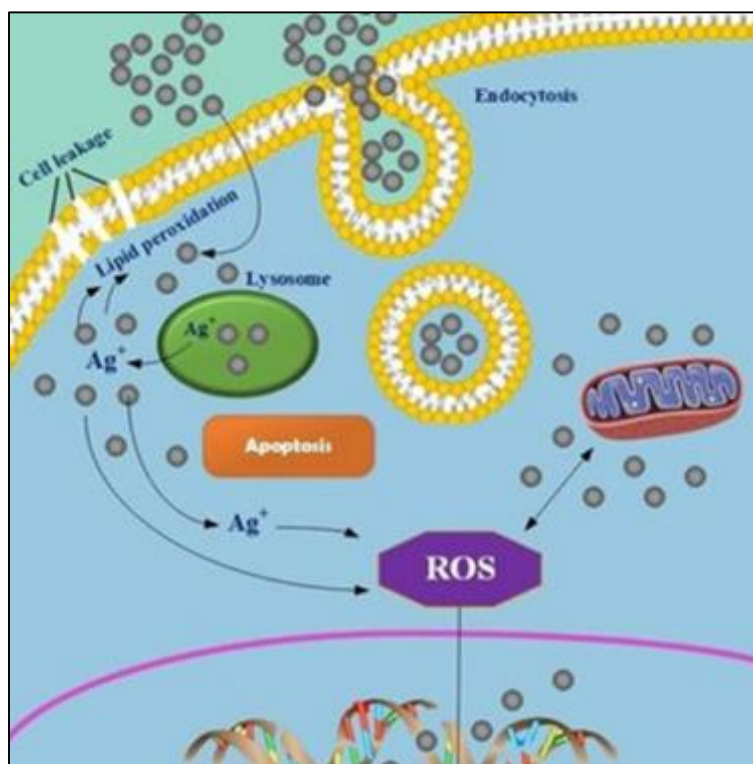


Figure 6 Schematic representation of the mechanism of anticancer effect of silver nanoparticles

Theranostic is defined a combination of diagnostics and therapy. The bio-synthesized AgNPs could be used in theranostic applications including anti-cancer therapeutic agent, drug delivery and bioimaging vehicle. Green AgNPs can be used as beneficial theranostic agents for further discovery of various biomedical applications [58-59]. AgNPs, which were biosynthesized with various applications, were tested in different cancer cell lines. summarizes the recent studies comparing potential therapeutic approaches of AgNPs on different cancer types. Currently, the production of many toxicological data related to nanoparticles occasionally causes an adverse perception of their use Nevertheless, toxicity may be helpful in cancer treatments because the cytotoxic effect is desirable for cancer cells. Many studies suggest that positive results have been obtained when incorporating silver nanoparticles into cancer therapies. New

properties of silver nanoparticles and rapidly changing new application fields are emerging along with the increase in the number of scientific studies. In particular, the development of different techniques for the synthesis of silver nanoparticles leads to enlarge the application fields in medicine. It is thought that silver nanoparticles produced by green biosynthesis using plant extracts or microorganisms may be more suited to clinical approaches than the physical or chemical methods. Additionally, green Biosynthesis of AgNPs is a simple, safe, cost effective and eco friendly approach. Because of all these reasons, green silver nanoparticles seems to be a promising anti-cancer agent in the field of medicine. But, further researches need to enhance its selectivity on cancer cells, and to determine biocompatibility and side effect in animal models. [60]

4.5. Wound healing

Damage to the skin's and the surrounding tissues' natural structure is referred to as a wound. This type of damage can result from a variety of stressors, such as mechanical or physical harm, chemical or thermal damage, or biological impairment. Immediately following the occurrence of a wound, the natural healing process begins with the remarkable local recruitment of immunological, cellular, and vascular components that work in concert to properly restore structural and physiological functioning [61,62]. The proper order of the following crucial steps is necessary for this process to occur: tissue remodeling, cellular proliferation, re-epithelialization, hemostasis, and inflammation [63, 64]. The wound healing process is insufficient when the afflicted tissue is unable to heal adequately, which can result in a number of complications and even fatal disorders. There aren't many approaches accessible right now for the clinical care of wounds. For example, skin autografts and xenografts offer a superior healing process and compatibility.

An ideal treatment option for deep wounds. These tactics have several drawbacks in addition to being costly, like limited bioavailability, heightened immunogenicity, and heightened potential for disease transmission [65, 66]. Furthermore, oxygen-enriched therapy helps hasten wound healing since oxygen is necessary for the induction of angiogenesis, the stimulation of collagen production, and subsequent re-epithelialization. In addition to being an expensive and difficult process, hyperbaric oxygen therapy was found to have limited effectiveness since negative pressure therapy is typically more appropriate for minor wounds and can have a number of physical adverse effects that could impede the healing process [67, 68]. Using wound dressings is another therapeutic approach for wound healing. They help the injured tissue's structural and functional recovery and may also offer defense against external pathogens. A few important points: Biocompatibility, fluid (super)absorption, oxygen and water partial permeability, nonimmunogenicity, and easy, nontraumatic removal are all factors that need to be taken into account for a successful wound dressing [69, 70]. The current trend in wound care management, despite the large range of commercially available dressings, is to produce customized and performance-enhanced dressings that offer appropriate compositional, structural, and biofunctional properties for a proper wound healing process [71, 72].

Stabilized with AgNPs functionalized with juglone, highly ordered collagen scaffolds were assessed as beneficial substrates for intercellular adhesion and cell adhesion. Alginate and nanocrystalline cellulose scaffolds that have been combined with nanosilver to create extremely elastic, absorbent macroporous scaffolds with significant antibacterial benefits for use in wound treatment [73]. AgNPs-impregnated BC/polydopamine scaffolds were suggested as a treatment for burn injuries; the resulting nanostructured scaffolds demonstrated notable antiproteolytic and proangiogenic properties, leading to accelerated and improved wound healing [74].

Bergonzi et al. recently proposed 3D-printed plate healing. Being evidenced after 25 days. The nanocomposites facilitated necrotic tissue clearance, promoted Collagen deposition and epidermis neof ormation. The scaffolds also determined increased/decreased Levels of anti-inflammatory/pro-inflammatory interleukins, respectively, and upregulation of growth Factor genes involved in wound healing [75]. Highly antimicrobial electrospun PLA scaffolds Modified with nanosilver and cellulose nanofibrils promoted the proliferation and normal growth Of ocular epithelial cells, with no proinflammatory reaction. The hydrophilic scaffolds were recently Proposed as effective ocular bandages. AgNPs and lavender oil-induced synergistic antibacterial Effects when incorporated within polyurethane (PU) nanofibrous scaffolds. The resulted hydrophilic Nanocomposites encouraged improved proliferation and normal development of fibroblasts [76]

4.6. Tissue Engineering

Human tissues are made up of extremely ordered cells with distinct roles and an extracellular matrix (ECM, protein-based environment) that surrounds them at the microstructural level. containing glycosaminoglycans, which control intercellular communication, adjust cell physiology, and give three-dimensional support for cellular adhesion and proliferation. In general, acute or chronic traumas, severe inflammatory illnesses, hereditary disorders, degenerative conditions, and malignancies can all result in the structural and functional degradation of human tissue. Healthcare professionals and scientists turned to tissue engineering's impressive potential in an attempt to overcome the

limitations of organ transplantation, which included reduced bioavailability in the case of autografts and isografts, immunogenicity and graft rejection in the case of allografts and xenografts.

As a part of regenerative medicine, the desideratum of tissue engineering (TE) is represented by the fabrication of nonviable complex biocompatible systems that are able to revive the structural integrity and functionality of damaged tissues by restoring, replacing or regenerate them [77]. Nanostructured biomaterials represent a suitable choice for TE applications, not only because they properly interact with living systems and possess specific and selective therapeutic purpose, but also because they possess versatile and tunable characteristics which enable the achievement of particular requirements, such as (i) biocompatibility (a complex feature that relies on the bidirectional interactions between nanomaterials and host cells or tissues); (ii) physicochemical properties (microstructure, phase transitions, porosity, wettability, morphology, topography, composition, stability, reactivity); and (iii) circumstantial bioactivity [78, 79].

Given their reduced toxic effects in healthy cells, facile surface functionalization and excellent antimicrobial activity, the impact of nanosilver-based biomaterials for TE was thoroughly evaluated. To begin with, AgNPs-embedded coatings were reported to boost the biological performances of bioinert materials used in orthopedics and orthodontics. The simple modification of titanium implants' surface with nanosilver resulted in significant antibacterial effects against strains responsible for implant-associated infections while maintaining excellent biocompatibility [80-82].

5. Conclusions

Numerous physicochemical parameters, including size, shape, concentration, surface charge, and colloidal state, have been linked to the intrinsic antimicrobial effects exhibited by silver nanoparticles (AgNPs). Additionally, the impressive available surface of AgNPs allows the coordination of numerous ligands, opening up enormous possibilities with regard to the surface functionalization of AgNPs. AgNP-based nanosystems and nanomaterials are suitable alternatives for drug delivery, wound dressing, tissue scaffold, and protective coating applications.

Numerous studies have demonstrated the advantageous benefits of AgNPs in innovative biocompatible and nanostructured materials and gadgets created for contemporary medicinal approaches.

AgNPs have additional mechanical, optical, chemical, and biological characteristics that make them desirable for the development, acquisition, testing, and clinical evaluation of performance-enhanced biomaterials and medical devices in addition to their appealing and adaptable antibacterial potential. Nevertheless, in-depth research is needed to determine their toxicity over the short and long terms as well as the processes underlying these effects.

The remarkable potential of silver nanoparticles in biomedical applications is outlined by the current constraints associated with traditional healthcare practice and the most recent difficulties brought about by nanosilver-based technology. AgNPs are excellent candidates for reaching the very close modern biomedicine desired outcome, whether we take into account the creation of new nanostructured biomaterials and devices or the modification of existing ones.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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