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Antimicrobial effective nanoparticles: Mechanisms and recent achievements

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Abstract

Multiple drug resistance in bacteria has become one of the most important global public health concerns in the last few decades. Existing antimicrobials could be inadequate in the treatment of infections caused by multiple antibiotics-resistant bacteria. Research on the development of inexpensive and effective antimicrobials has gained importance recently. Nanotechnology is a promising alternative in the development of new antimicrobials, as in other fields of science. The antimicrobial effects of nanoparticles alone and antimicrobiotics bound to nanoparticles on multiple drug-resistant microorganisms will be discussed in detail. As the treatment of resistant microorganisms with existing agents becomes inadequate, new treatment searches have begun. Considering the long and expensive production processes of a new treatment agent, inexpensive and effective new solutions have become sought after, and it has come to the fore to increase the effectiveness of the existing one and make it effective in the target area. Antimicrobial-based metal nanoparticles are used extensively in various cancer types as they are valuable in tumor detection, early diagnosis, and targeted delivery of chemotherapeutic agents. Metal nanoparticles are used as important agents in cancer therapy as they are easily penetrating cells and they are non-toxic to tissues. In this review, nanoparticles that have antimicrobial, antibiofilm effects, and drug delivery systems are discussed with their effect mechanism and different application fields.

Keywords: Antimicrobial agents, nanoparticles biofilm, multiple drug resistance, cancer

Introduction

The increase in multidrug resistance (MDR) in pathogenic microorganisms (bacteria, fungi, viruses, and parasites) that cause infections in humans and animals has reached the alarm level. All health organizations report that this increase should be stopped urgently [1]. Current antimicrobials (antibiotics, antifungals, antivirals vs) may remain insufficient in the treatment of infections caused by multidrug-resistant (MDR) microorganisms (superbugs) [2]. The lack of innovation in the development of new antibiotics undermines the fight against drug-resistant infections [1]. Nanotechnology is a promising alternative to combat multidrug-resistant (MDR) microorganisms. Advantages of nanomaterials can be listed as; some nanomaterials may have antimicrobial effects, hence, new antimicrobials can be developed. Nanomaterials are quite good nanocarriers for existing antibiotics because of their specific properties. They can prevent the formation of biofilms on the surfaces, so that, increasing the effect of antimicrobials is expected. In summary, nanoparticles have some advantages due to their easily penetration to the bacterial membrane, preventing biofilm formation or being an effective antimicrobial carrier [3].

Using nanotechnology in the analysis of nanoscale structures, in understanding the physicochemical properties of these structures, in their synthesis, production, and creation of new application areas with the use of these materials provides great benefits [4]. With the improving nanotechnology, new and different structures with different physical and chemical properties have emerged at the atomic and molecular levels. When working with sizes smaller than 100 nm, it is possible to develop smaller, cheaper, lighter, more useful, and qualified devices or materials. By reducing the size of the device or material, it is ensured that the energy cost is reduced and it becomes more convenient for use. The reason for the widespread use of nanoparticles is that they exert high effects of quantum size, their electronic structure is size-dependent, surface atoms have different characteristic properties and they have a high surface /volume ratio. Due to the extraordinary properties of these structures, nanoparticles synthesis is used in the preparation of many

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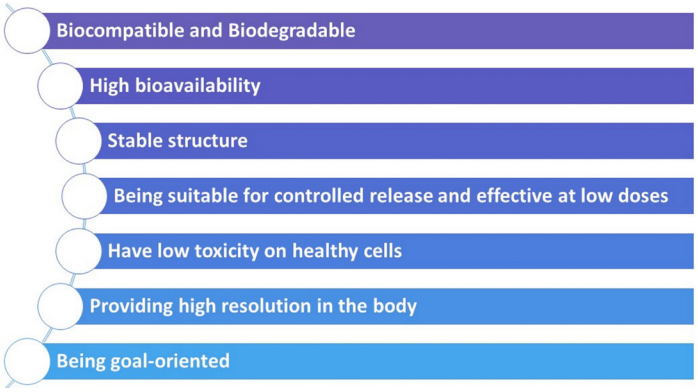
technological and pharmacological products such as high-activity catalysts, special technological materials for optical applications, additives against wear, drug carriers, superconductors, surfactants, and special diagnostic tools. In addition to these areas of use, nanoparticles allow the creation of miniaturized devices with specific functions such as nano control of materials, nanocarriers, sensors, nanomachines, and high-density data storage cells. Due to their unique features; nanoparticles, are preferred in many fields in medicine, industry, and technology [5].

We can list features of nanoparticles (Scheme 1) as follows:



Scheme 1. General properties of antimicrobial nanoparticles

Metals, metal oxides, polymers, and silicates are widely used in the synthesis of nanomaterials [5]. Nanomaterials can be in rod, spherical, cubic, helical, cylindrical shapes, etc. They can be found in quite different structures. These structures can be designed with application-oriented modifications. In this way, it has a great role in being one of the most important application areas of nanotechnology. Nanoparticles are divided into two groups inorganic and organic nanoparticles. Magnetic and metal (silver, platinum, gold, palladium, copper, etc.) nanoparticles and semiconductor nanoparticles (such as zinc, titanium oxides) from inorganic nanoparticles. Some nanoparticular enzymes have an antimicrobial activity that can overcome resistance mechanisms such as enzyme activation, decreased cell permeability, modification of enzymes, and excessive pumping of flow pumps, and can be good alternatives to antibiotic drugs. The large surface area/volume ratio increases the area of interaction with the target area. They can also increase the inhibitory effects of antibiotics. On the other hand, a combination of antibiotics and nanoparticles can also create complex antimicrobial mechanisms. Nanoparticles catch great interest from each major department of medicine because of their quality to deliver drugs in the optimum dosage range due to the increased therapeutic efficiency of the drugs, improved patient compliance, and weakened side effects [5]. Generally, the selection of optimum nanoparticles for biological and cell imaging studies depends on their optical features. Iron oxide is the most preferred metal nanoparticle in biomedical fields (cell separation, immunoassay, tissue repair, detoxification of biological fluids hyperthermia) [5]. Nanoparticles in the form of the polymer structure such as polyethylene oxide and polylactic acid have been commonly used in the intravenous administration of drugs [5]. The detection of analytes or compounds in tissue parts can be achieved by labeled antibodies with radioactive compounds, colloidal gold nanoparticles, fluorescent dyes, and enzymes [5].

Drug distribution is becoming more and more important for the treatment of human diseases. As nanotechnology has found its use in medicine, nanoparticle drug deliveries have attracted great attention over the past few years due to their unique chemical, physical, biological, and structural properties. The incorporation of drug molecules into the nanocarrier can protect a drug from degradation and also offers targeting and controlled release possibilities. Nanocarriers can be modulated to accumulate in target tissues through surface functionalization or by controlling particle size, and therefore drug-loaded nanocarriers can be used to selectively deliver an active ingredient to a particular part of the body. This allows a lower dose to be administered and in this way toxicity due to accumulation can be avoided.

Cancer is a disease characterized by uncontrolled cell growth and is a third leading cause of mortality all over the world. Conventional cancer treatments like radiotherapy or chemotherapy often result in several side effects and also drug resistance is a major problem in many malignant tumors. The nanoparticle-based drug delivery approach has an important role in simultaneous diagnosis and treatment. Gold and silver nanoparticles have been utilized for cancer therapy for a while with their excellent surface chemistry, high surface area/volume ratio, multi-functionalization, and stability. They are also easily penetrating to cells and their accumulation in the body does not cause any toxicity.

Antimicrobial nanoparticles have been also so popular in dentistry applications. They have been preferred due to their large surface area. These nanoparticles could be used as filling materials, adhesives, and in some restorations of teeth [6].

In this paper, we focused on antimicrobial nanoparticles in tumor detection, imaging, photothermal and photodynamic therapy as part of anti-cancer treatment [7]. Nanoparticles are explained in detail with their antimicrobial effects, their role as drug carriers, and preventing biofilm formation. Applications of antimicrobial nanoparticles in different fields have been discussed in detail.

Antimicrobial effects of nanoparticles

Infections caused by gram-positive bacteria such as vancomycin-resistant Enterococcus faecium (VRE), methicillin-resistant Staphylococcus aureus (MRSA), and gram-negative bacteria such as multidrug-resistant Klebsiella pneumonia, Acinetobacter baumannii are one of the most important health problems. Antibacterial features of several metals, metallic oxides, and metallic salts are known for centuries. Silver (Ag), gold (Au), copper (Cu), bismuth (Bi) metals and metal oxide nanoparticles such as magnesium oxide (MgO), iron oxide (Fe3O4), zinc oxide (ZnO), copper oxide (CuO), and titanium dioxide (TiO2) are considered for antimicrobial therapy (Figure 1) [8]. Antibacterial effects of these nanoparticles are oxidative stress, metal ion release, enzymatic inhibition, formation of reactive oxygen species (ROS), protein denaturation, altering gene expression with DNA damage, and disruption of the cell wall and cell membrane structures [9].

Maghimaa and Alharbi demonstrated that the silver nanoparticles (AgNPs) produced from Curcuma longa leaf, are tested as antibacterially effective against pathogenic microorganisms such as Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pyogenes, and Candida albicans [5]. AgNPs deliver Ag + ions and

can catalyze the production of toxic oxygen radicals for bacteria. Oxygen radicals can disrupt microbial molecular structures such as proteins/enzymes [10]. Riaz Rajoka et al. biosynthesized AgNPs mediated by exopolysaccharide via Lactobacillus Brevis MSR104 isolated from Chinese koumiss. Biosynthesized AgNPs had antimicrobial activity against E. coli and Staphylococcus aureus and the activity of AgNP-nisin conjugates to Bacillus subtilis, Staphylococcus aureus, Proteus Vulgaris, and Escherichia coli were investigated. Growth kinetics studies (live/dead BacLight bacterial viability test) were performed in these bacteria with control, nisin, AgNP, and nisin-AgNP conjugates. It has been determined that AgNP-nisin conjugates were most effective against bacteria.

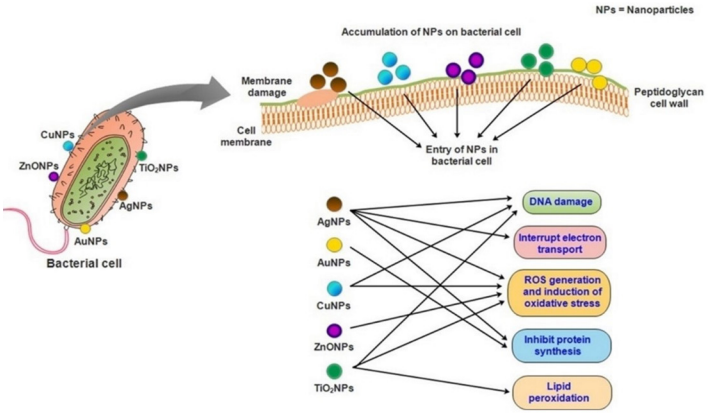


Figure 1. Representation of various antibacterial mechanisms for different nanoparticles. Represented by permission from Elsevier [58]

In one study, the investigation of the antimicrobial activity of silver nanoparticles has been presented which have been synthesized from the extract of the Corchorus Capsularis leaf. They reported that AgNPs had significant antibacterial activity against multidrug-resistant (MDR) Pseudomonas aeruginosa, Staphylococcus aureus, and CoNS strains isolated from postoperative wound infections. Cavassin et al. (2015) found that citrate and chitosan AgNPs showed maximum antimicrobial activity against 54 isolates including oxacillin-resistant S. aureus, carbapenem, and polymyxin-resistant Acinetobacter baumannii, carbapenem-resistant Enterobacteriaceae, vancomycin-resistant Enterococcus spp. The antimicrobial activity of AgNPs is also higher against Gram-negative microorganisms compared to Gram-positive MDR resistant strains. On the other hand, AgNPs synergistically enhance the antibacterial effects of antibiotics, including penicillin G, amoxicillin, vancomycin, clindamycin, and erythromycin against S. aureus and E. coli isolates [12]. In an in-vivo animal study, it was shown that the use of local biogenic silver nanoparticles in the postoperative treatment of abscesses caused by Corynebacterium pseudotuberculosis in small ruminants reduced the risk of postoperative infection and provided rapid recovery. In addition, no evidence of poisoning was observed in animals [13] because of nanoparticles consumption. The bactericidal properties of AgNPs are strikingly affected by particle shape, size, concentration, and colloidal state. These properties appear to increase biocompatibility and stability [14].

There are some studies about the effect of AgNPs on fungi [15]. AgNPs have been found to effectively inhibit yeast growth at concentrations much lower than their cytotoxic limits (about 1 mg / L) against human fibroblasts [16]. AgNPs biosynthesized from aqueous leaf extract have an anti-candida effect and antibiofilm activity. In addition, they are not toxic to the MCF-7 cell line and primary mouse bone marrow-derived mesenchymal stem cells (mBMSCs) [15]. Milanezi et al. (2019) evaluated the antimicrobial activities of quercetin-coated gold nanoparticles for S. aureus, B. cereus, E. coli, S. Typhimurium, and Aspergillus fumigatus (three clinical isolates) and reported that they have strong antifungal effects. Golden nanoparticles (AuNPs) with sophorolipid cap (AuNPs-SL) have antibacterial action against bacteria (especially for Gram-negative bacteria), act synergistically with different antibiotics, minimize side effects, and degrade microbial biofilm [17]. Metal nanoparticles (AgNP and AuNP) biosynthesized from petal extract of saffron (Crocus sativus L.) inactivated many pathogenic bacteria and fungi such as Staphylococcus aureus, Bacillus cereus, Escherichia coli, Aspergillus, and Candida albicans. On the other hand, the antibacterial effect of photosynthesized AgNPs was higher than AuNPs [18]. The myco-synthesized cobalt oxide nanoparticles (Co3O4NPs) from Aspergillus brasiliensis ATCC 16404 have an antibacterial effect against various pathogenic bacteria (Bacillus subtilis, S. aureus, P. aeruginosa, Escherichia coli) [19]. Recently, many studies have been carried out on the antimicrobial, antioxidant and toxic properties of metal nanoparticles biologically synthesized from extracts of plants licorice root [20], Jasminum auriculatum leaf [21], Cryptolepis Buchanani Roem plant [22], Curcuma longa L. [10] and extracellular metabolites of marine bacteria [23] and extract of Sargassum plagiophyllum macroalgae [24]. These are summarized in Table 1.

The Minimum Inhibitory Concentrations (MICs) of titanium dioxide nanoparticles (TDNPs) alone and in combination with antibiotics (amikacin, ciprofloxacin, ceftriaxone, and cefepime) were investigated against multidrug-resistant P. aeruginosa isolates. Adding TDNPs to tested antibiotics has shown that these antibiotics have a positive effect on therapeutic activity. It has also been reported that the addition of TDNPs will increase antibacterial activity in the development of topical antibiotics [3]. Numerous studies have been carried out about the antimicrobial effects of both salts and biosynthesized forms of ZnO NPs on E. coli, Klebsiella pneumoniae, Staphylococcus aureus, Methicillin-Resistant Staphylococcus aureus, Enterococcus bacteria [25]. They reported that ZnO NPs are effective against these bacterial species.

The role of antimicrobial nanoparticles as an antibiotic carrier

Organic nanoparticles such as lipid-based nanoparticles, liposomes, polymeric nanoparticles; inorganic nanoparticles such as silica nanoparticles, metallic nanoparticles such as silver, gold nanoparticles conjugated with antibacterial drugs can be used as delivery systems. Nanosystems have important physicochemical properties such as size, surface electric charge, and solubility, which are extremely important for the drug's effect on microorganisms in drug therapy. Antibiotic efficiency is positively affected by the number of used antibiotics, range of use, dose. Infections can be treated quickly before drug resistance develops [26]. Nanosellulose based NPs conjugated with antibacterial (allicin, polymyxin B, ceftriaxone, ampicillin, gentamycin) have been used for the investigation of antibacterial activity [27]. In addition, studies on oral and topical use of antibiotics containing

Amphotericin B, using lipid-based nanocarriers, have shown to be promising [28]. In one study, antimicrobial peptide encapsulated with dextran nanoparticles was applied to the lungs as aerosol, and the antibiotic duration and treatment were significantly improved [29]. A study on the efficiency of cefotaxime coated with gold AuNPs was found effective on a CTX-M-15 positive cefotaxime resistant Escherichia coli and Klebsiella pneumonia [30]. For over fifty years, amphotericin B (AmB), a broad-spectrum polyene antibiotic has also been used in the treatment of invasive fungi and the treatment of visceral leishmaniasis. AmB acts by destroying the cell membrane. amphotericin B- deoxycholate (AmB-DOC), the conventional formulation is highly nephrotoxic. Therefore, the use of new lipid nanocarriers for AmB delivery has been explored over the last five years [31]. It has been emphasized that the safety and efficiency of oral and topical lipid nanocarrier AmB administration in animal models of fungal infections and leishmaniasis is promising.

The role of antimicrobial nanoparticles in preventing biofilm formation

Nanoparticles could be used as effective candidates in treating bacterial infections and preventing biofilm-producing pathogenic bacteria in environmental or industrial settings [32]. Balakrishnan et al. determined that AgNPs, which are biosynthesized in Nutmeg aqueous seeds, are effective on Salmonella enterica serovar Typhi biofilm isolated from typhoid patients and asymptomatic carriers. In another study, Klebsiella oxytoca DSM 29614 isolate produces AgNPs embedded in the exopolysaccharide in the presence of Fe (III) -citrate and Ag+. These AgNPs have been reported to inhibit Staphylococcus and Pseudomonas biofilm formation [33]. Palanisamy et al. determined that AgNPs prevented biofilm formation in multidrug-resistant strains of Pseudomonas aeruginosa. In the multi-drug resistant strains of 105 and 106 CFU/mL, the biofilm inhibition of AgNPs at a concentration of 20 µg/mL was highest. Therefore, they reported that AgNPs can be used to reduce the severity of multi-drug P. aeruginosa infections [34].

In another study, nanosilver inhibited biofilm production and growth in reference strains of S. epidermidis. In this study, the antibiofilm activity of AgNPs in 10 to 100 nm sizes and concentrations of 1 to 10 µg/mL was investigated. The highest efficacy against these strains was demonstrated by a particle size of 10 nm and a nanosilver at a concentration of 5 µg/mL [35]. As a result of this study, the dimensions of the applied nanoparticles were found to be important for the inhibition of biofilm formation.

In conclusion, there are many recent studies (Table 1) on the antimicrobial and antibiofilm activities of nanoparticles and their use of effective antimicrobials delivery systems. Moreover, there are lots of studies that have reported the positive effects of nanoparticles.

Table 1. The effects of antimicrobial nanoparticles

Nanoparticles	Microorganisms	Effect	References
Nanoparticles combined with antibiotic and antimicrobial agents			
Cefotaxime loaded AuNPs	CTX-M-15 positive cefotaxime resistant E. coli, K. pneumoniae	Effective against cefotaxime resistant strains	[30]
AgNPs and AuNPs conjugated cefixime	S. aureus	Antimicrobial	[15]
AuNP Sophorolipid capped	Vibrio chlorea	Antibacterial and antibiofilm	[17]
Biosynthesized nanoparticles and antimicrobial effect			
AuNPs and AgNPs from extract of saffron (Crocus sativus L.)	A. niger, C. albicans, S. aureus, E. coli	Antibacterial and antifungal	[23]
AuNPs from Licorice root extract	B. subtilis, S. aureus, E. coli, P. aeruginosa, S. Typhi, P. citrinum, C. albicans, A. flavus	Antibacterial and Antifungal	[21]
AuNPs from of S. plagiophyllum (algae)	S. Typhi, E. coli	Antimicrobial	[24]
AuNP from Cryptolepis buchanani Roem plant	S. aureus, Metisilin Resistant Staphylococcus aureus (MRSA) Acinetobacter baumanii	Antimicrobial	[22]
AuNP using the stem of Tinospora cordifolia	Pseudomonas aeruginosa	Antibiofilm	[15]
AgNP loaded cotton fabrics from Curcuma longa L.	S. aureus, P. aeruginosa	Antimicrobial	[10]
AgNP from aqueous seeds extract of Myristica fragrans (nutmeg)	MDR Salmonella enterica serovar Typhi	Antibiofilm	[32]
AgNP EPS NPs produced by K. oxytoca	S. aureus, P. aeruginosa	Antibacterial antibiofilm	[33]
AgNP exopolysaccharide mediated	E. coli, S. aureus	Antimicrobial	[60]
ZnONP	E. coli	Antibacterial	[25]
AgNP	S. epidermidis,	Antibiofilm	[35]
TiONP	MDR P. aeruginosa	Antibacterial and synergistic	[3]

AgNP, silver nanoparticle; AuNP, gold nanoparticle; IONP, iron oxide nanoparticles; ZnONP, zinc oxide nanoparticles; TiONP, titanium oxide nanoparticles; SSPS based NC, curcumin loaded soy soluble polysaccharide based nanocarriers; BIF, boron imidazolate framework; E.coli, Escherichia coli; K.pneumoniae, Klebsiella pneumoniae; S.aureus, Staphylococcus aureus; B.cereus, Bacillus cereus; S.Typhimurium, Salmonella Typhimurium; A.fumigatus, Aspergillus fumigatus; A.niger, Aspergillus niger; C.albicans, Candida albicans; B.subtilis , Bacillus subtilis; P.aeruginosa, Pseudomonas aeruginosa; P.citrinum, Penicillium citrinum; A.flavus, Aspergillus flavus; S.pyogenes, Streptococcus pyogenes; L.lecanii, Lecanicillium lecanii; T.viride, Trichoderic viride; S.plagiophylum, Sargassum plagiophylum; MRSA, methicillin-resistant Stapyhlococcus aureus; A.baumanii, Acinetobacter baumanii; A.nidulans, Aspergillus nidulans ; T.biforme, Trichaptum biforme; P.italicum, Penicillium italicum; F.oxysporum, Fusarium oxysporum; C.gloeosporioides, Colletotrichum gloeosporioides; C.freundii , Citrobacter freundii; L.monocytogenes, Listeria monocytogenes; S.epidermidis, Staphylococcus epidermidis; S.Paratyphi, Salmonella Paratpyhi

Applications of Antimicrobial Nanoparticles

Applications of Antimicrobial Nanoparticles in Drug Delivery Systems

In recent years, nanotechnology has become important as drug delivery research has shifted from micro-scales to nanoparticles (Figure 2) [21]. Nanocarriers usually called nano-sized as designed, these systems have unique physical, chemical, biological and structural properties that provide effectiveness because of several advantages for drug delivery [36]. Nanocarriers have been designed as drug delivery systems with improved pharmacological and therapeutic properties compared to conventional drugs. The incorporation of drug molecules into the nanocarrier can protect a drug from degradation and also offers targeting and controlled release possibilities [36]. By confining the drug buildup only in the target area, they can reduce the toxicity and undesirable effects that can result from accumulation in other tissues. Nanocariants can comfortably cross the blood-brain barrier (BBB) and operate at the cellular level. Physicochemical properties such as particle size, material content, and system structure are thought to be effective in transporting to the brain. While the mechanism of brain transport is not understood, another point of view is that transport occurs by mimicking agents that can cross the brain barrier. For example, in the study of Narayani and Rao, polysorbate-coated nanoparticles of low-density lipoprotein (LDL) were thought to mimic this by making a trip through the brain capillary wall and allowing you to move the LDL receptor [37].

Compared to traditional drug forms, nano-carrier-drug conjugates are more effective and selective. Haque et al. in their studies with alginate nanoparticles showed that the Venlafaxine (VLF) loaded alginate nanoparticles had a higher rate of blood/brain than the VLF solution used intranasally and intravenously. The superiority of nanoformulation of the direct transport of VLF in the treatment of depression has been demonstrated. In another research, Román et al. prepared alginate microcapsules in the outer part of which epidermal growth factors were attached. Cisplatin (carcinogenic drug) was loaded into the prepared nanoparticles. They used this nanoformulation to target non-small cell lung cancer cells. They stated that with the addition of EGF, faster cell (h460-lung cancer strain) death kinetics were observed compared to free drug and the specificity of delivery systems increased significantly [38–42]. Metallic nanoparticles, lipids (LDC (lipid-drug conjugated systems), NLC (nano formed lipid carriers), SLN (solid lipid nanoparticles) and liposomes), polymers (anti-HIV zidovudine used to treat loaded polylactide/chitosan, broad-spectrum used in the treatment of tumors, doxorubicin-loaded PEGylatedPLGA – PEGylated poly (lactic-co-glycolic acid) and tacrine-laden chitosan used to treat Alzheimer's), dendrimer and micellar substances (chitosan, alginate, etc.)) silicon or carbon materials and magnetic nanoparticles such as nano-gel various nano-drug delivery systems, cardiovascular defects, autoimmune diseases, HIV, Alzheimer's, and cancer, including treatment options for a wide variety of problems have been evaluated as drug carriers, and proved to be functional (Figure 3) [36].

Liposomal systems are approved by the FDA and are considered one of the best drug delivery systems as they present membrane structures similar to cell membranes and facilitate the inclusion of drugs within them [40]. But, unlike other systems such as metal nanoparticles; liposomes, micelles, and dendrimers, they have some surface properties like SPR (surface plasmon resonance). For example, Prusty and Swain synthesized a system of covalently bonded silver with a spongy polyacrylamide/dextran nano-hydrogel that releases 98.5% ornidazole. Surface functionalization due to silver resulted in high biocompatibility [43].

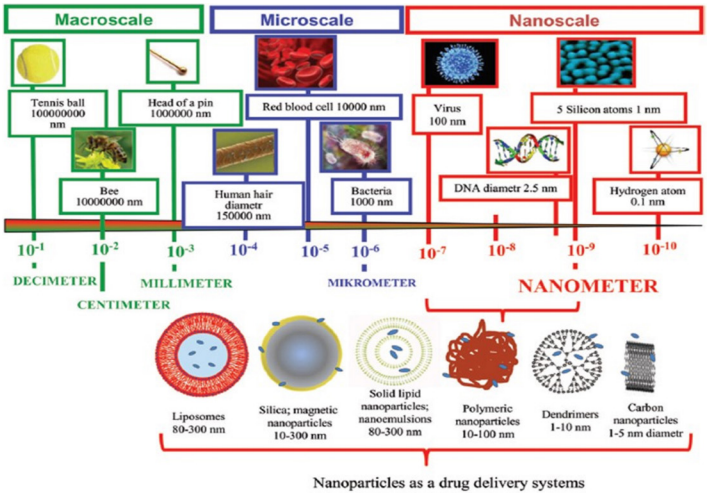


Figure 2. Nanoparticle drug delivery systems with relation to other scales. Represented by permission from Elsevier [42]

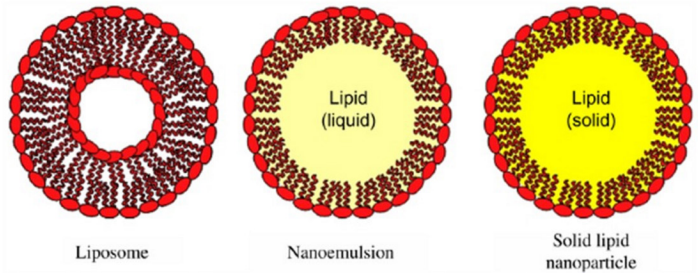


Figure 3. Lipid-based nanoparticles. Represented by permission from Elsevier [59]

Anticancer Therapy

Cancer is defined as a disease ongoing with abnormal cell growth with the potential to invade or spread to multiple parts of the body. Cancers are a group of aggressive and hard-to-treat diseases and they affect millions of people all around the world. In the year 2019, about 18 million new cases were reported and 8.8 million deaths/year are associated with cancer [44]. Especially with some types of cancer, the conventional radiotherapy and chemotherapy regimens mostly fail because of the drug resisting nature of the disease. Also, the drugs currently used for anti-cancer treatments are toxic to the other cities of the body, they mostly produce side effects or adverse effects on normal body physiology, decreasing the effectiveness of the treatment.

Cancer nanomedicine is a term referred to the field of research including the development of NPs as part of anti-cancer treatment. Metal NPs are classified as highly bioavailable, safe, and nontoxic agents of cancer therapy. AuNPs and AgNPs can be used alone or coated with a polymer in combination with conventional anti-cancer therapies. AuNPs and AgNPs have shown promising results in cancer diagnostics and therapeutics up to date. Although they might exert different effects on cells; metal nanoparticles share the same mechanisms of action over malignant cells by similar

cellular processes. Besides their anti-cancer effects, antimicrobial nanoparticles can also be used for supporting and enhancing the effects of chemotherapy and radiotherapy. Their nanometric size range is also a primary advantage as they can cross easily across blood capillaries and even the blood-brain barrier. Both AuNPs and AgNPs are taken up by endocytosis, the vesicles are distributed in the cytoplasm and nucleus producing toxic effects leading to apoptosis (programmed cell death), accumulation of reactive oxygen species (ROS) and by altering endothelial growth factors and pro-inflammatory cytokines like TNF – Tumour necrosis factor, VEGF – Vascular endothelial growth factor, and Interleukin-6 [45].

AgNPs

AgNPs shows one of the most extensively preferred categories of nanomaterials. These nanoparticles have a significant role in the diagnosis of malignant tumors and they are also used in controlled drug delivery systems. AgNPs are suitable for cellular uptake by cancer cells in terms of morphology. Likewise, their antimicrobial activity, uptake of AgNPs by cancer cells depend on mechanisms like receptor-mediated endocytosis or phagocytosis [46]. Once they are internalized; they induce oxidative stress as a result of Ag ion release which in turn cause the death of cancer cells, by inducing apoptosis (by activating pro-apoptotic genes like Bax) or by causing functional deficits in subcellular compartments like mitochondrial malfunction, production of reactive oxygen species (ROS), cell cycle dysregulation, formation of chromosomal abnormalities and DNA damage. There are various recent studies about AgNPs in the literature. Kanipandian et al. have reported increased mitochondrially-derived apoptosis in lung adenocarcinoma by silver nanoparticle registration. It was also shown recently that A549 lung cancer cell lines treated with biosynthesized AgNPs overexpressed the pro-apoptotic caspase-3 gene [47].

AgNPs are also proved to have anticancer efficiency against human colon and breast cancer cell lines. In a comparative study performed by Ahn et al.; nanosilver particles made by various plant extracts have been shown to cause cytotoxicity against lung cancer cells [48]. Majeed et al. reported that bacteria-mediated biosynthesized nanosilver capped with bovine serum albumin showed significant toxicity against breast, colon, and osteosarcoma cancer cells. The apoptotic mechanisms were obtained by the study of Almalki et al. in which silver nanoparticles synthesized from Bacillus sp KFU36 and its anticancer effect in breast cancer MCF-7 cells [49]. In other recent studies; AgNPs biosynthesized with extract of Nepeta deflersiana medicinal plant against human cervical cancer cells and also Sinigrin-mediated synthesized AgNPs and combined with Campthothecin were reported to cause increased oxidative stress, mitochondrial damage, and cell cycle impairment causing apoptosis and necrosis in tumor cells. AgNPs biosynthesized by freshwater cyanobacterium illustrated dose-dependent cytotoxic effects against colon cancer and human breast cells, again by the activation of pro-apoptotic processes [11]. There are also new studies in the literature that used AgNPs bio-reduced by Fusarium oxysporum strain; Penicillium citrinum strain; Bacillus safensis strain; Penicillium italicum strain; and Bacillus amyloliquefaciens strain have proven to cause apoptosis, membrane damage, and/or ROS accumulation in bladder, breast, hepatocellular, laryngeal and lung adenocarcinomas respectively. Besides their well-known apoptotic and oxidative stress-inducing mechanisms; AgNPs can also block tumor angiogenesis by restricting endothelial migration and proliferation by suppressing vascular endothelial growth factor-A (VEGF-A). AgNPs obtained with red amaranth extract caused a decrease in neovascularization in breast cancer cells [50]. Biosynthesized AgNPs with intrinsic cytotoxicity has proven to potentiate the effect of gamma radiation treatment in hepatic cancer cells. AgNPs capped with polyethylene glycol (PEG) and labeled with radioactive iodine, I-131 showed increased targeting for malignant tissues.

AuNPs

The AuNPs; like AgNPs show anti-cancer activities based on their metallic nature. The major ways in which AuNPs can be used in anticancerous therapy as photodynamic, photothermal, and anti-angiogenic. When the AuNPs are directly targeted to the nucleus, they can promote cell-cycle arrest which in turn activates apoptosis AuNPs are used as targeted drug delivery systems or can be combined with a therapeutic molecule to improve toxicity against cancer cells AuNPs that represent specific photo-optical properties have been used in photothermal and photodynamic therapy. Photothermal therapy emerges overheated cells by using non-ionizing energy sources such as lasers. AuNPs can be used as probes because of their strong SPR absorption in the near-infrared region. When exposed to the laser, the SPR band is converted to heat. The heat generated causes hyperthermia which leads to cell necrosis. In photodynamic therapy; a photosensitizer (e.g. 5-aminolevulinic acid (5-ALA)) is used; which first becomes excited and then reacts with molecular oxygen within cells and cause the formation of reactive oxygen species (ROS) that cause changes in structures of macromolecules like lipids, proteins, and nucleic acids and causes apoptosis (cell death). AuNPs have been used to deliver these photosensitizers specifically to the tumor cells in brain cancer models [51].

Au-Ag NPs

AgNPs and AuNPs have been tested for their toxic effects on different cancers both in vivo and in vitro. These composite nanomaterials can be synthesized in either of the two ways; Ag-coated Au and/or Au-coated colloidal particles. These mixtures exhibit some specific properties which are different from the single-metal NPs. In recent studies; they were proven to be substrates for Surface-Enhanced Raman Spectroscopy (SERS) and, that's why they can be used in detecting specific proteins and biomarkers in blood and several body fluids like CSF (cerebrospinal fluid) and may serve as detectors of early cancer biomarkers and also low drug levels. In another study, Au-Ag NPs were used in differential colorimetric detection of various DNA targets in a single system. Branched gold-silver nanoparticles coated with dopamine and subjected to near-infrared irradiation caused cytotoxicity in colon cancer cell lines again by causing apoptosis and necrosis [52]. NP-mediated photothermal therapy (PTT) was proven to exhibit excellent potential as contrast agents for fluorescence and computed tomography imaging by He et al.[53]. When chemotherapeutic and photothermal effects were combined after laser irradiation, increased cytotoxicity over cancer cells was reported for methotrexate-conjugated nanoparticles based on graphene oxide (GO) and AgNPs. Pothipor et al. have developed

a porous-hollowed-silver-gold nanoparticle labeling in the early diagnosis of prostate cancer with a quite low limit of detection [54]. Metal NPs are considered as promising anti-cancer agents as they are effective against drug-resistant malignancies and targeted drug delivery with their small size and easy penetration to various cell types (Figure 4) [55]. Besides these, they can be formulated in multiple ways like conjugation, coatings, drug encapsulation, bimetallic fusion, and they become potential candidates for treatments specific for cancer types or patients.

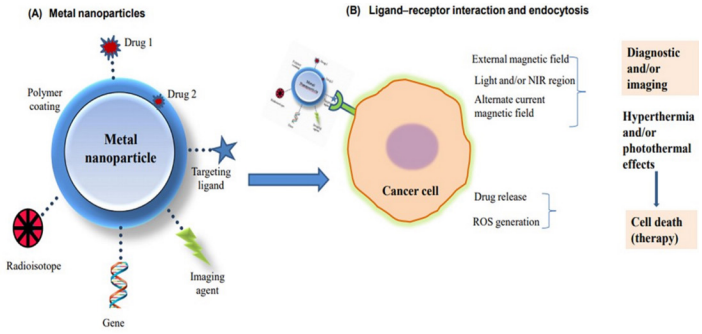


Figure 4. Schematic representation of ligand-receptor interaction between a metal nanoparticle and cancer cell. Represented by permission from Elsevier [55]

Applications of Antimicrobial Nanoparticles in Dentistry

Nanoparticles have been involved in the development of antimicrobial dental products such as filling materials, fissure sealants, cement, temporary restorations, and adhesives, due to their different size and other unique properties. The advantage of large surface interaction in metal nanoparticles is very effective in strengthening their antimicrobial properties. In the tooth; Nanoparticles are widely preferred in root canal cleaning, periodontal infection, removal of tooth sensitivity, caries control, and prevention of biofilm formation. Silver nanoparticles are widely preferred in dental applications due to their antibacterial effects and biocompatibility. Silver nanoparticles are also widely used in composite dental materials as light-sensitive components [56].

The use of nanoparticles in root canal disinfection processes increases the cleaning efficiency. Meirelles et al. found that when 0.02% silver nanoparticle gel was used, Enterococcus faecalis biofilm formation was reduced [57]. Increasing the hardness strength can be achieved by using materials such as diamond and sapphire to make the tooth structure more durable.

Conclusion

Nanotechnology, as in other fields of science, has brought a solution and innovative perspective to the field of medicine. Nanoparticles have unique physicochemical and biological properties compared to their larger counterparts and existing agents. The properties of nanoparticles can greatly affect their interaction with biomolecules and cells due to their specific size, shape, chemical composition, surface structures, charges, solubility, and physicochemical properties. In this review, we presented an overview of the antimicrobial activities (such as antibacterial, antibiotic, antifungal activities), types, uses, and applications of nanoparticles in infections caused by multiple drug-resistant microorganisms by taking part in drug transport such as metal nanoparticles or liposomal systems. In recent years, the use of metal nanoparticles as alternative and supporting therapy models in anti-cancer therapy has increased enormously. As the major problem in cancer therapy is drug resistance and toxic effects of conventional therapies on healthy cells; drug targeting with nanoparticles has gained much importance. The most commonly used metal nanoparticles are silver, gold, and silver-gold ones as they easily penetrate cells and they do not exert any toxic effects. The use of nanoparticles in drug targeting, imaging, early detection, and photothermal treatment of cancer increases every day. Nanoparticles can be used in combination with or as an alternative to conventional cancer therapies. As they improve the response of patients to cancer therapy and also patients' general status; these agents seem to be indispensable in the present and future of cancer therapy. Although most nanoparticle applications in medicine are aimed at drug delivery, they have been useful in many different and important applications. Antimicrobial applications in the treatment of important diseases such as cancer, dentistry, and other independent areas have begun to occupy a wide place and many studies have been conducted up to date.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

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