Review

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Nanosilver: an inorganic nanoparticle with myriad potential applications

Abstract: Bionanotechnology is the field dealing with the synthesis and application of different nanomaterials. Nanoparticles usually form the core of nanobiomaterials. For the past decade, a variety of inorganic nanoparticles have been newly created to provide superior material properties. Nowadays, synthesis of nanoparticles is the area of interest due to their physical, chemical, optical, electronic properties, and most importantly their larger surface area-to-volume ratio. Synthesis of inorganic nanoparticles is done by various physical and chemical processes, but biological route of synthesis is gaining more importance due to their eco-friendly nature. Bioactivity of nanoparticles broadly involves the wide range of nanoparticles and their biological application. They have been used as new tools not only for investigation of biological processes but also for sensing and treating diseases. In this respect, they are appearing to be novel antimicrobial agents even against drug-resistant microorganisms. On the other side at higher concentration, they show toxicity to the humans and ecosystem. Therefore, in the present review, we have briefly described the synthesis of different metal nanoparticles by different approaches mainly paying attention to their biosynthesis, antimicrobial activity, and cytotoxicity. As silver nanoparticles are finding many applications among all of the inorganic nanoparticles, we paid special attention to them, too.

Keywords: bioactivity; bionanotechnology; diversity; inorganic nanoparticles; toxicity.

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1 Introduction

Nanotechnology is concerned with development and utilization of structures and devices with organizational features at the intermediate scale between individual molecules and about 100 nm where novel properties occur compared to bulk [1]. One nanometer (1 nm) is the one billionth part of a meter (10^{-9} m). To put that scale in another context, the comparative size of a nanometer to a meter is same as that of the marble to the size of the earth. Nanotechnology has capability to build up tailored nanostructures and devices for given function by control at the atomic and molecular level. It is recognized as an emerging and enabling technology of the 21st century, in addition to the already established areas of information technology and biotechnology. Nanotechnology is expected to open some new aspects to fight and prevent disease using atomic scale tailoring of materials [1].

Nanomaterials are at the top of the rapidly developing field of nanotechnology. The development of reliable experimental protocols for the synthesis of nanomaterials over a range of chemical composition, size, and high monodispersity are the challenging issues in current nanotechnology [2]. There is an enormous interest in the synthesis of nanomaterials due to their unusual optical [3], chemical [4], photo-electrochemical [5], and electronic properties [6]. Different kinds of nanomaterials have been developed as per the need for application purpose. Nanoparticles exhibit a number of special properties relative to bulk material and often have unique visible properties because they are small enough to confine their electrons and produce quantum effects. The physicochemical, optical, and electronic properties of nanoparticle are the

result of quantum confinement. Research on nanoparticles is currently an area of intense scientific research. Various strategies have employed to synthesize different inorganic nanoparticles. To develop pollution-free strategies for biosynthesis of nanoparticles, biotechnology plays an important role and hence is called as "bionanotechnology."

This review is focused on the progress of bionanotechnology in terms of synthesis of nanoparticles and its bioactivities with special reference to antimicrobial activity. Here, we discuss the method of synthesis of nanoparticles and possible mechanism of antimicrobial activity against bacteria, fungi, and viruses. Moreover, we also explained the cytotoxicity of metallic nanoparticles.

2 Different methods of synthesis of nanoparticles

Different methods like physical, chemical, and biological have been employed for the synthesis of metal nanoparticles.

2.1 Physical synthesis

Synthesis of metallic nanoparticles by the physical methods involve different approaches such as ball milling, aerosol technology, lithography, arc discharge, laser ablation, microwave irradiation by UV and IR radiations, etc. Typically, these techniques require the use of some stabilizer to protect nanoparticles against agglomeration. Laser ablation known as liquid phase pulsed laser ablation (LP-PLA) technique is used to produce a wide range of novel materials, such as nano-diamond and related nanocrystals, metallic nanocrystals, nanocrystal alloys, and metal oxides [7]. Silver and gold nanoparticles were prepared by laser ablation of silicon (Si) target immersed in a water solution of respective metal salts ($AgNO_3$ and $HAuCl_4$) [8]. Laser ablation in combination with the laser, induces size control to nanoparticles, and provides versatile fully physical preparation method for gold nanoparticles with a broad size distribution of gold metal plate in an aqueous solution of sodium dodecyl sulfate (SDS) [9].

One of the most efficient physical methods for the preparation of nanoparticles was arc discharge. This method was found to be economical for the synthesis of metal nanostructure in which there was no necessity of metal catalyst, explosive, corrosive gases, or vacuum equipment. Si nanowires and nanoparticles have been produced by this method, using only arc discharge between two Si electrodes submerged in water [10]. The photolysis process with nanosecond laser excitation in a silver colloidal solution has recently been used for synthesis of nanoparticles, where as Courrol et al. [11] proposed the method for formation of silver nanoparticles using UV-LED, xenon lamp, and sodium lamp excitation prior to nanosecond laser irradiation. Recently, Manikprabhu and Lingappa [12] reported the microwave-assisted green synthesis of silver nanoparticles.

2.2 Chemical synthesis

A wide range of techniques to fabricate nanoparticles have been developed rapidly over the past decade. There are diverse approaches for the preparation of the nanoscale materials that have been reported in the literature. Some of these methods include controlled chemical reduction by ionic surfactant, electrochemical reduction, metal vaporization, sonochemical processing, solvent extraction reduction, micro-emulsion technique, polyol processes, alcohol reduction, etc.

There are evidences which demonstrate that chemical methods are more effective as they provide better control over size, shape, and functionalization [13]. Reduction of metal salt in the presence of suitable capping agents such as polyvinyl pyrrolidone (PVP) is the common method to generate metal nanocrystals. Solvothermal and other reaction conditions were also employed for the synthesis, to exercise control over their size and shape of the nanocrystals [14, 15]. Silver and gold nanoparticles were prepared by a simple hand grinding method by using ethylene glycol and poly vinyl alcohols as dispersion stabilizer [16]. Sun and Luo [17] and Amendola et al. [18] had developed method for production of silver nanoparticles without using any reducing and stabilizing agent.

Icosahedral Au nanocrystals were obtained by the reaction of $HAuCl_4$ with PVP in aqueous media [19]. Right bipyramidal nanocrystals (75–150 nm) of Ag have been prepared by the addition of NaBr during the polyol reduction of $AgNO_3$ in the presence of PVP [20]. Cu nanoparticles of pyramidal shape have been synthesized by electrochemical procedure [21]. Synthesis of $FeNi_3$ nanoparticles by ambient chemical reduction were reported by Hongxia and group [22]. Similarly, nanoparticles of Rh and Ir were successfully prepared by the reduction of the appropriate compound in the ionic liquid, 1-n-butyl-3 methylimidazolium hexafluorophosphate, in the presence of hydrogen [23].

Metals like Au and Ag have almost identical lattice constant, which was responsible for a strong tendency toward the alloy formation. The bimetallic particles will be in core shell or alloy forms depending on the preparation

conditions, miscibility, and kinetics of reduction of metal ions. Au-Ag was reported to form homogeneous alloy when reduced simultaneously. One step ahead, Au/Ag/Au double shell nanoparticles were reported to synthesize by continuous micro segmented flow synthesis [24]. Pal et al. [25] developed reverse micelle method using nonionic surfactant Triton X-100 for the preparation of Ag, Au, and Ag-Au alloy nanoparticles. Micro-emulsion technique was one of the most important methods to prepare nanoparticles. Micro-emulsion may be defined as a thermodynamically stable isotropic dispersion of two immiscible liquid consisting of nanosize domains of one or both liquids in the others, stabilized by an interfacial film of surface active molecule. The dispersion phase consists of monodispersed droplets in the range of 10–100 nm [26, 27]. SDS micro-emulsion system was widely used in the past to prepare metal nanoparticles, Cu-Ni alloy [28], Pd [29], and Ag [30, 31]. Zhang et al. [27] have employed SDS quaternary micro-emulsion to prepare nanometer-sized nanoparticles by mixing two micro-emulsion containing the precursor silver nitrate and hydrazine, respectively. They reported that bigger micro-emulsion droplets have a tendency to give larger particles. Charinpanitkul et al. [32] prepared ZnS nanoparticles from quaternary micro-emulsion system.

There are several examples for the reduction of metal salts by organic solvent; gold [33], silver [34], and platinum [35] nanoparticles were synthesized by this method. Sun and coworkers demonstrated the polyol method for the production of Ag nanowires and nanoprisms by reducing $AgNO_3$ with ethylene glycol in the presence of seeds and polyvinyl pyrrilidone [36, 37]. Santos and Liz-Marzan [38] reported the ability of N,N-dimethyl formamide (DMF) to reduce Ag^+ ions, so that stable spherical Ag nanoparticles can be synthesized using PVP as stabilizer. Similarly, various other chemical approaches have been used for the synthesis of different metal nanoparticles like copper iodide [39], zinc oxide [40], ZnS-Co-doped [41], and gold [42].

2.3 Biological synthesis

Other than physical and chemical methods mentioned above, biological methods (use of biological systems) are also being used for the synthesis of inorganic nanoparticles. These methods score some advantages over the physical and chemical methods, and therefore, gaining more importance in the fabrication of nanoparticles. Many biological systems like bacteria, actinomycetes, algae, fungi, and plants have been used for the intra- and extracellular synthesis of metal nanoparticles.

2.3.1 Bacterial synthesis

Some well-known examples of bacteria synthesizing inorganic metal nanoparticles include magnetotactic bacteria, which synthesize iron oxide nanoparticles [43, 44], diatoms, which synthesize siliceous materials [45], and S-layer bacteria, which produce gypsum and calcium carbonate layers [46]. The gold particles of nanoscale dimensions can be readily precipitated within bacterial cells by incubation of the cells with Au^{3+} ions, which was demonstrated by Beveridge and coworkers [47]. Silver nanoparticles of well-defined size and distinct morphology within the periplasmic space of the bacteria may be formed when bacterial culture isolated from silver mine (*Pseudomonas stutzeri* AG259) was placed in a concentrated aqueous solution of $AgNO_3$. It resulted in the reduction of the Ag^+ ions and formation of silver nanoparticles [48, 49]. Nair and Pradeep [50] showed that nano-crystals of gold, silver, and their alloys can be synthesized by reaction of the corresponding metal ions within cells of lactic acid bacteria present in buttermilk.

Later, extensive study has been done in the field of bacterial synthesis of different kinds of inorganic nanoparticles. It includes the synthesis of gold nanoparticles from *Rhodopseudomonas capsulata* [51], cyanobacteria [52], *Brevibacterium casei* [53], gold nanocubes from *Bacillus licheniformis* [54], silver nanoparticles from *K. pneumoniae*, *Escherichia coli*, and *Enterobacter cloacae* [55], *B. licheniformis* [56], *Bacillus* sp. [57], *Salmonella typhimurium* [58], lactic acid bacteria [59], cadmium sulfide nanoparticles from *E. coli* [60], *Rhodopseudomonas palustris* [61], selenium nanospheres from selenium respiring bacteria [62].

2.3.2 Actinomycetes

Ahmad and coworkers [63] reported the intracellular biosynthesis of gold nanoparticles. *Rhodococcus* sp. was used (an alkalotolerant actinomycetes) for synthesis of nanoparticles. The gold nanoparticles obtained showed a good monodispersity with size ranging from 5 to 15 nm. The particles were found on the cell wall as well as on the cell membrane but in a larger amount in the former. This observation was probably due to reduction of the gold ions by enzymes present in the cell wall and cell membranes. The metal ions were not toxic to the cells, and they remained viable even after the reduction of gold ions. Ahmad and coworkers [64] have also reported the extracellular synthesis of gold nanoparticles by chemical reaction of the biomass with chloroaurate ions. Formation of

a high concentration of gold nanoparticles of an average size of 8 nm was observed.

2.3.3 Yeasts

The biosynthesis of quantum crystallites in yeast has been reported in *Candida glabrata* and *Schizosaccharomyces pombe* cultured in the presence of cadmium salt [65]. Kowshik and coworkers [66] reported the intracellular synthesis of cadmium sulfide nanoparticles by *S. pombe* strain when challenged with 1 mM cadmium solution. The CdS nanoparticles exhibited an absorbance maximum at 305 nm. X-ray scattering data showed that the nanoparticles had Wurtzite (Cd16S20) type hexagonal lattice structure and most of the nanoparticles were in the size range of 1–1.5 nm. Extracellular synthesis of silver nanoparticles was observed in silver tolerant yeast strains MKY3 when challenged with 1 mM soluble silver in the log phase of growth [67]. It was shown that silver was not reduced when the supernatant of MKY3 culture (grown in the absence of silver) was exposed to an environment of silver ions. *Saccharomyces cerevisiae*-mediated biosynthesis of gold nanoparticles was also reported [68].

2.3.4 Algae

The brown alga *Fucus vesiculosus* was reported for the bioreduction of Au (III) to Au (0) into gold nanoparticles of different sizes and shapes when exposed to dilute hydrometallurgical solutions and leachates of electronic scraps at pH7 [69]. *Rhizoclonium fontinale* and *Ulva intestinalis* were reported to produce gold nanoparticles intracellularly [70]. Biological reduction and extracellular synthesis of nanoparticles were achieved in 120 h at 37°C at pH 5.6. Nanoparticles in the range of 7–16 (silver), 6–10 (gold), and 17–25 nm (bimetallic 50:50 ratio) were synthesized, which were analyzed by transmission electron microscopy, while XRD analysis confirm the silver and gold nanoparticles formation of metallic silver and gold. Fourier transformed infrared spectroscopic measurements proved that protein is responsible for reduction of metal ions to nanoparticles. Green synthesis of gold nanoparticles using the algae extract of seaweed *Turbinaria conoides* was carried out. Preliminarily confirmation was done from the color changing from yellow to dark pink in the reaction mixture, and from the broad surface plasmon resonance band centered at 520–525 nm. Transmission electron microscopy confirmed the formation of polydispersed gold nanoparticles with the size range of 6–10 nm [71]. Kalabegishvili et al. [72] reported the reduction of chloroaurate ($HAuCl_4$) into gold nanoparticles when exposed to blue-green algae *Spirulina platensis*. Recently, Singh et al. [73] reported the extracellular biosynthesis of gold nanoparticles using *Padina gymnospora*, this approach was found to be rapid and less time consuming. In another study by Jena and coworkers [74], synthesis of silver nanoparticles using fresh extract and whole cell of microalga *Chlorococcum humicola* was reported.

2.3.5 Mycosynthesis

Mycosynthesis is the synthesis of nanoparticles by fungi. The term "mycosynthesis" was for the first time used by Ingle et al. [75] to describe synthesis of nanoparticles by *Fusarium acuminatum*. Rai and coworkers [76] proposed the term "myconanotechnology" to include research carried out on nanoparticles synthesized by fungi. Myconanotechnology is the boundary between mycology and nanotechnology. After the extensive literature survey carried out, it is clear that the fungal systems are the better alternatives for the synthesis of metal nanoparticles. Many fungal species have been explored for the production of different metal nanoparticles of different shapes and sizes. Fungi may have the potential to provide relatively quick and ecologically "clean" biofactories for metallic nanoparticles [76]. *Colletotrichum* species, an endophytic fungus growing in the leaves of geranium produces gold nanoparticles when exposed to chloroaurate ions. These particles were predominantly decahedral and icosahedral in shape, ranging in size from 20 to 40 nm, this was experimentally reported by Shivshankar et al. [77]. Lichen fungi (*Usnea longissima*) have shown synthesis of bioactive nanoparticles (usnic acid) in specified medium used. The synthesized nanoparticles were found in the range of 50–200 nm [78].

Shivshankar and coworkers [77] reported the use of geranium leaves (*Pelargonium graveolens*) and its endophytic fungus in the extracellular synthesis of gold nanoparticles. In their experiment, they have treated sterilized geranium leaves and an endophytic fungus (*Colletotrichum* sp.) with aqueous chloroaurate ions. In both cases, rapid reduction of the metal ions was observed, which resulted in the formation of stable gold nanoparticles of variable size. In case of geranium-mediated synthesis, the gold nanoparticles were appeared to be capped by terpenoids, whereas they were identified as polypeptides/enzymes in case of *Colletotrichum* sp.-mediated synthesis. The gold nanoparticles synthesized by fungi were found to be spherical in shape, whereas these particles synthesized

by using plant leaves were found to be rod, flat sheets, and triangular in shapes. Chen et al. [79] studied the extracellular formation of silver nanoparticles using *Phoma* species. Some soil-borne fungi like *Aspergillus fumigatus* were reported to produce the silver nanoparticles extracellularly, when the cell extract was challenged with aqueous silver ions [80]. Gade et al. [81] reported the biosynthesis of silver nanoparticles from the *Aspergillus niger* isolated from soil and also suggested the mechanism for the action of silver nanoparticles on the *E. coli*.

Out of different fungal genera used for the synthesis of nanoparticles, the genus *Fusarium* was found to be used many times. Ahmad et al. [82] for the first time used the *Fusarium oxysporum* for the synthesis of silver nanoparticles and gave a new vision to the fungal nanotechnology. They have reported that aqueous silver ions when exposed to the fungus *F. oxysporum*, get reduced in solution, thereby leading to the formation of an extremely stable silver hydrosol. The silver nanoparticles were in the range of 5–15 nm in dimensions and stabilized in solution by proteins secreted by the fungus. It is believed that the reduction of the metal ions occurs by an enzymatic process.

Bansal et al. [83] found that after exposure of *F. oxysporum* to an aqueous solution of K_2ZrF_6 result in the protein-mediated extracellular hydrolysis of the zirconium hexafluoride anions at room temperature. It leads to the formation of crystalline zirconia nanoparticles. Duran et al. [84] studied the extracellular production of metal nanoparticles by several strains of the fungus *F. oxysporum*. They found that aqueous silver ions when exposed to several *F. oxysporum* strains are reduced in solution, thereby forming silver hydrosol. The silver nanoparticles were in the range of 20–50 nm in dimensions. Similarly, other *Fusarium* species like *F. oxysporum* strain 5115 [85], *F. semitectum* [86], *F. acuminatum* [75], *Fusarium solani* [87] and *Fusarium culmorum* [88], *Cryphonectria* sp. [89], *Humicola* sp. [90], *Penicillium citrinum* [91], as well as other *Fusarium* species [92] for silver nanoparticles, *A. niger* [93] for gold nanoparticles, *F. oxysporum*. *F*. sp. *lycopersici* for platinum nanoparticles [94], *F. oxysporum* for zirconia nanoparticles [83] have been successfully used. Other fungal species used for the production of metal nanoparticles includes *Trichoderma viride* [95], *Penicillium fellutanum*, and *Penicillium purpurogenum* [96] for silver nanoparticle synthesis [97].

2.3.6 Plants

Gardea-Torresdey and coworkers [98] reported the formation of gold nanoparticles inside live alfalfa plants, when alfalfa plants were grown in $AuCl_4$-rich environment. The absorption of Au metal by the plant was confirmed by X-ray absorption studies (XAS) and TEM. Atomic resolution analysis confirmed the nucleation and growth of Au nanoparticles inside the alfalfa plant. Armendariz et al. [99] studied oat (*Avena sativa*) biomass as an alternative to recover Au^{3+} ions from aqueous solution and for its capacity to reduce Au^{3+} to Au^0-forming Au nanoparticles. To study the binding trend of Au^{3+} to oat and the possible formation of Au nanoparticles, the biomass and a solution of Au^{3+} were reacted for a period of 1 h at pH values ranging from 2 to 6. Persimmon (*Diopyros kaki*) leaf extract helps to make Au and Ag nanoparticles of 15–90 nm size, the study was carried out by Song and Kim [100].

Sathishkumara and coworkers [101] reported the synthesis of nanocrystalline palladium particle of size 15–20 nm from *Cinnamomum zeylanicum* bark extract. Similarly, Smitha et al. [102] used *C. zeylanicum* leaf broth as the reducing agent for the production of gold nanoparticles. Krishnaraj et al. [103] studied the biosynthesis of silver nanoparticles and its activity on water-borne bacterial pathogens. Silver nanoparticles were rapidly synthesized using leaf extract of *Acalypha indica* and the formation of nanoparticles was observed within 30 min. High-resolution transmission electron microscopy (HRTEM) analysis showed 20–30-nm-sized nanoparticles. Antibacterial activity of synthesized silver nanoparticles showed effective inhibitory activity against water-borne pathogens viz., *E. coli* and *Vibrio cholerae*. Silver nanoparticles in 10 μg/ml concentration were recorded as the minimal inhibitory concentration (MIC) against *E. coli* and *V. cholerae*.

Rai et al. [104] reviewed that plants as a biological system for the fabrication of nanoparticles have emerged as simple, cost-effective, and eco-friendly and rapid technique. They also proposed that plant is a good source for the synthesis of quantum dots. Gade et al. [105] reported silver nanoparticles synthesis by *Opuntia ficus-indica*. They evaluated antibacterial activity against *E. coli* and *Staphylococcus aureus* in combination with ampicillin, gentamycin, kanamycin, streptomycin, and vancomycin. Antibacterial activity of a commercially available antibiotic was increased in combination with silver nanoparticles as it already has bactericidal activity. They also proposed the mechanism for the synthesis of silver nanoparticles that quercetin present in a high concentration was responsible for the synthesis of silver nanoparticles. Bonde et al. [106] synthesized silver nanoparticles by the leaf extract of *Murraya koenigii* (Indian curry leaf tree), which showed antibacterial activity against various types of bacteria. Similarly, some other plants like *Solanum*

tricobatum, *Syzygium cumini*, *Centella asiatica* and *Citrus sinensis* [107], *Moringa oleifera* [108], *Coleus aromaticus* [109] for silver nanoparticles, and *Ananas comosus* [110] have been used for the synthesis of gold nanoparticles.

3 Diversity in bioactivity of silver nanoparticles

Bioactivity broadly involves a wide range of biological applications of nanoparticles. For the past decade, a variety of inorganic nanoparticles have been newly created or modified to provide superior material properties with functional versatility. Simultaneously, due to their size features similar to biological species (e.g., proteins, viruses, and genes) and potential advantages over existing chemical imaging agents, these nanoparticles have been used as new tools not only for investigation of biological processes but also for sensing and treating diseases.

Nanoparticles usually form the core of nanobiomaterials. These nanobiomaterials can be used as convenient surface for molecular assembly [111] and may be composed of inorganic or polymeric materials. The spherical-shaped nanoparticles are often used, but some other like cylindrical, plate-like are also being used. The nanoparticle size and size distribution might be important in some cases, for example, penetration through a pore structure of cellular membrane requires small size and uniform nanoparticles. Similarly, narrow size distribution of sizes allows creating very efficient fluorescent probes that emit narrow light in a very wide range of wavelength. This helps to produce biomarkers with many and well distinguished color [111].

Quantum dots [112], gold nanoparticles [113], and superparamagnetic nanoparticles [114] were the most promising nanostructures for *in vitro* diagnostic applications. These nanoparticles can be conjugated to recognition of moieties such as antibodies or oligonucleotides for detection of target biomolecules. Nanoparticles have been also utilized in wide range of biological application like immunoassays, immunohistochemistry, DNA diagnostics, bioseparation of specific cell populations, and cellular imaging. Nanoparticle-based diagnostics may open new frontiers for detection of tumors, infectious diseases, bioterrorism agents, and neurological diseases [115]. Metallic nanoparticles have been used as strategies to deliver conventional pharmaceuticals or substances such as peptides, recombinant proteins, vaccines, and nucleotides. The silver, gold, and magnetic nanoparticles are important carriers for new pharmaceutical formulations [116]. Some parasitic diseases such as malaria, schistosomiasis, trypanosomiasis, leishmaniasis, tuberculosis, leprosy, filiarasis, etc., yet have not received any attention by public. In such disease liposomes, polymeric nanoparticles and nanostructured lipid carriers have been applied. These nanocarrier systems showed promising results in the treatment of such parasitic diseases with diminished toxicity and increased efficacy and prolonged release of drug with reduced number of dosage [117]. Solid lipid nanoparticles, polymeric nanoparticles, liposomes, micelles, functionalized nanoparticles, nanotubes, and metallic nanoparticles have been used to deliver conventional pharmaceutical drugs or biological molecules such as recombinant protein, enzymes, vaccines, nucleotides [118]. Being excellent carriers for biological molecules, nanoparticles can improve the therapeutic efficiency.

Single quantum dot of compound semiconductors was successfully used as a replacement of organic dyes in various bio-tagging applications [112]. Quantum dots were also used in *in vivo* imaging of breast cancer cells expressing HER2 protein [119]. Jiang et al. [120] reported the use of quantum dots in detection of genomic aberrations of cancer genes by fluorescence *in situ* hybridization (FISH). Inorganic nanoparticles were used in labeling of macrophages expressing mannose receptors and *in vivo* cancer imaging [121]. Quantum dots and gold nanoparticles were widely used in immunohistochemistry to identify protein-protein interaction [122]. It can be used in labeling DNA or proteins for detection of biological targets. They are also primarily utilized in imaging, immunoassay, and molecular diagnostic applications [123, 124].

Supermagnetic nanoparticles were made of magnetic materials such as iron, nickel, cobalt, or alloys of magnetic metals. The nanoparticles exhibit the phenomenon of super magnetism where thermal energy is sufficient to change the direction of magnetization of the nanoparticles [125]. Ultra small supermagnetic iron oxide particles used as contrast agents not only have greater magnetic susceptibility but also more widespread tissue distribution because of their ultra small size, which facilitate their uptake in various tissues. Artemov et al. [126] used streptavidin-conjugated superparamagnetic resonance molecular imaging of HER2/neu receptors expressed by breast cancer cells. Superparamagnetic nanoparticles can also be used to separate pathogenic cells from normal cells [127]. In addition, there are many more applications of inorganic nanoparticles, which are given below.

4 Antimicrobial activity of inorganic nanoparticles

4.1 Antimicrobial activity of silver nanoparticles

Silver is a naturally occurring precious metal. It has been used for thousands of years for preparing ornaments, utensils, jewelry for trade, etc. Nowadays, silver metal has been used in a wide array of applications including electrical contacts and conductors, in mirrors, and in chemical reaction catalysis. The antimicrobial properties of silver have been known from ancient days. Ancient civilizations were aware of silver's bactericidal properties [128]. Metalic silver is relatively inert and poorly absorbed by mammalian or bacterial cells. Similar to other heavy metals, silver is toxic to microorganisms by poisoning respiratory enzymes and components of the microbial electron transport system and impairing some DNA function [129, 130]. *In vitro* studies provide evidence for the bactericidal effect of silver, which is attributable largely to the binding of the silver ion to free sulfhydral group of proteins or on its surface leading to inactivation of the enzyme phosphomannose isomerase. Owing to the discovery of several antibiotics, the use of silver compounds has been declined remarkably. Nowadays, there is growing concern about the emergence and re-emergence of drug-resistant pathogen such as bacterial strains, fungi, and parasites [131]. Therefore, the development of new antimicrobial compounds, or the modification of those available to improve their antimicrobial activity, is the necessity of time and this is in high priority of research. Owing to its broad spectrum activity, efficacy, and lower costs, the search for newer and superior silver-based antimicrobial agents was necessary. Therefore, it has been used in the different formulations such as silver nitrate, silver sulfadiazine for the treatment of several microbial infections, in burn cases, etc. Among the various alternatives available, silver nanoparticles have been in focus and are being considered as a precursor and an excellent candidate for therapeutic purposes.

4.1.1 Antibacterial activity

As mentioned above, in metallic state, silver is inert, but when it comes in contact with moisture, it gets ionized. The ionized silver is highly reactive, when it binds to tissue proteins; it brings structural changes in the bacterial cell wall and nuclear membrane leading to cell distortion and death. Silver also binds to bacterial DNA and RNA and inhibits bacterial replication by denaturing it [132, 133]. Feng et al. [134] carried out mechanistic study of silver ions against *S. aureus* and *E. coli* by treating those with silver nitrate, and the effects on cell morphology were studied by using electron microscopy. In the case of *E. coli*, various morphological changes were observed after treatment of silver ions. There was detachment of cytoplasmic membrane from cell walls and electron light region observed in the center of the cytoplasm, which contains condensed form of DNA. Condensed form of DNA occurs due to protecting it from the silver ion injury. Small electron dense granules surrounding the cell wall or deposited inside the cell were also observed. *S. aureus* showed the similar morphological changes like *E. coli*. The only difference found in the case of *S. aureus* is that electron dense granules surrounding cell wall and electron light region was darkening compared to *E. coli*. *S. aureus* has a stronger defense system due to the thicker peptidoglycan compared to Gram-negative *E. coli*. Thus, a thicker cell wall protects the cell from the penetration of silver ions in the cytoplasm. The proposed possible mechanism for the silver ion action was that the silver ion penetrates through the cell wall, and the DNA gets condensed, which reacts with the -thiol groups of protein and results in cell death [134].

In a similar direction, antimicrobial activity of silver nanoparticles against Gram-negative *E. coli* was studied by Sond and Sondi [135]. Silver nanoparticles interact with the building blocks of the bacterial membrane and damaged the cells. Silver nanoparticles reside in the cell membrane confirmed by the TEM and energy-dispersive X-ray analyses (EDAX), which showed the formation of pits on the cell surface. Baker et al. [136] reported that the silver nanoparticles were cytotoxic to *E. coli* cell at 8 μg/ml concentration. The antibacterial activity of silver nanoparticles was due to increased surface area-to-volume ratio. Susceptibility constants of *E. coli* and *Bacillus subtilis* to silver and copper nanoparticles were defined by Yoon et al. [137] and were used for determining the nanoparticle concentration required to achieve a target antibacterial efficiency. *E. coli* and *B. subtilis* were entirely inhibited at the concentration >70 μg/ml and 60 μg/ml for silver and copper nanoparticles, respectively. The result showed that *B. subtilis* was more sensitive than *E. coli* to nanoparticles. One possible reason for the lower sensitivity of *E. coli* was that the outer membrane of Gram-negative bacteria, for example, *E. coli* mainly consists of tightly packed lipopolysaccharide molecules, which provides an effective resistive barrier against nanoparticles.

Morones et al. [138] studied the effect of size and different concentrations of silver nanoparticles against Gram-negative bacteria using angled annular dark field microscopy and transmission electron microscopy. The concentration above 75 μg/ml showed no significant growth. Scanning transmission electron microscopy showed the presence of silver nanoparticles in the cell membrane and inside the bacteria, whereas high angled annular dark field images showed that the smaller-sized nanoparticles has efficient antibacterial activity, and thus, it showed size-dependent antimicrobial activity. Another mechanism was proposed by Lok and colleagues [139]; according to them, even a short exposure of silver nanoparticles to *E. coli* cell resulted in alteration in the expression of a panel of envelope and heat shock protein. Therefore, these particles can penetrate and disrupt the membranes of bacteria, loss of intracellular potassium was induced, and ATP level decreased. The phospholipid integrity of the cell membrane also may be the site of action for the silver nanoparticles. All these effects culminate in the loss of cell viability. A possibility of free radical involvement near the silver nanoparticle surface in its antimicrobial activity was proved by electron spin resonance (ESR) measurement. Relationship between antibacterial activity and free radical was demonstrated by the antioxidant NAC test. The result of test suggested that the free radical may be derived from the surface of silver nanoparticles and responsible for the antimicrobial activity [140]. Shrivastava et al. [141] proposed the mechanism for the antimicrobial activity of silver nanoparticles by analyzing phosphotyrosine profile of bacterial protein. The major mechanism through which silver nanoparticles manifested antibacterial properties was by anchoring to and penetrating the bacterial cell wall and modulating cellular signaling by dephosphorylating putative key peptide substrates on tyrosine residues. Pal et al. [25] investigated the antibacterial properties of silver nanoparticles of different shapes. They found the inhibition of bacterial growth by spherical nanoparticles at silver content of 12.5 μg/ml, and in the case of triangular nanoparticles, bacterial inhibition observed at 1 μg/ml. These findings confirmed that the antibacterial activity of silver nanoparticles is shape dependent.

Streptococcus mutans causes dental caries, which is a well-known public health problem throughout the world. Sierra et al. [142] compared the bactericidal and bacteriostatic effects of silver, zinc oxide, and gold nanoparticles. They used nanoparticles of silver, zinc oxide, and gold with an average size of 25 nm, 125 nm, and 80 nm, respectively, prepared by colloidal solution with oversaturation of salt. The result interpreted that the nanoparticles of silver, compared to gold and zinc oxide showed maximum antibacterial activity at lower concentration, and hence, silver nanoparticles were most effective for controlling *S. mutans* and ultimately dental caries. Silver nanoballs with a concentration 40 μg/ml demonstrated complete bactericidal properties against *E. coli*, *S. typhimurium*, *B. subtilis*, and *Pseudomonas aeruginosa*. The antimicrobial activity of nanoballs was due to the overall negative charge on the bacterial cell at physiological pH. The pH values were negative because of excess number of carboxylic groups, which upon dissociation makes cell surface negative. The opposite charges developed attract each other due to electrostatic forces. Nanoballs on entering the bacteria, inhibit the cell wall synthesis, damage the cytoplasmic membrane, inhibit nucleic acid and protein synthesis, inhibit specific enzyme systems, which results in the inhibition of complete bacterial cell [143]. Li et al. [144] studied the synergistic antibacterial effects of β-lactam antibiotic and silver nanoparticles. They used amoxicillin as a β-lactam antibiotic, and on increasing the concentration of both amoxicillin (0–0.5 mg/ml) and silver nanoparticles (0–40 μg/ml), antibacterial effect was enhanced. When amoxicillin and silver nanoparticles were combined, it results in greater bactericidal efficiency on *E. coli* cells than when they were applied separately. Test confirms that combining amoxicillin with silver nanoparticles resulted in a synergistic antibacterial effect on *E. coli* cells. The synergism was probably caused by a binding reaction between amoxicillin molecules, which exhibit groups such as hydroxyl and amido groups that can react easily with silver nanoparticles. The silver nanoparticles probably operate as an antibiotic carrier. Shahaverdi et al. [145] studied the combined effect of silver nanoparticles with different antibiotics. Silver nanoparticles were synthesized by *K. pneumoniae*, and its antibacterial activity was investigated against *S. aureus* and *E. coli*. It was observed that the antibacterial activity of antibiotics enhanced in the combination of silver nanoparticles. The highest synergistic activity was observed with erythromycin against *S. aureus*.

Similarly, Ingle et al. [75] studied the antibacterial activity of mycosynthesized silver nanoparticles from *F. acuminatum* against four human pathogenic bacteria including multidrug-resistant *S. aureus* and found that the mycosynthesized silver nanoparticles showed efficient antibacterial activity in all four bacteria. Birla et al. [146] reported the synergistic activity of antibiotics and silver nanoparticles against multidrug-resistant bacteria. They investigated that silver nanoparticles in

combination with antibiotics enhance their antibacterial activity against *S. aureus*, whereas *E. coli* is resistant to ampicillin and vancomycin, but when these antibiotics combined with silver nanoparticles, they showed antibacterial activity. Similarly, *P. aeruginosa* resistant to ampicillin, streptomycin, and vancomycin was inhibited by antibiotics when combined with silver nanoparticles. Antibacterial activity of commercially available antibiotics was increased in the presence of silver nanoparticles against *K. pneumoniae* and *Enterobacter aerogenes*. The increase in fold area is due to the synergistic activity of antibiotics and silver nanoparticles. As the silver nanoparticles showed the synergistic activity with different antibiotics, they can be used in combination with commercially available antibiotics for the development of effective antimicrobial agent [88]. Pattabi et al. [147] have evaluated antibacterial activity of silver nanoparticles against selected Gram-negative bacteria viz. *E. coli* and *P. aeruginosa* and Gram-positive bacteria viz. *S. aureus* and *Streptococcus pneumoniae*.

Shameli et al. [148] investigated the significant antibacterial activity of different sizes of nanosilver against Gram-positive (*S. aureus*) and Gram-negative bacteria (*S. typhimurium* SL1344) by the disc diffusion method using Müeller-Hinton Agar. Silver nanoparticles found to have broad spectrum activity against a variety of Gram-positive and Gram-negative bacteria. Devi and Joshi [149] screened 53 isolates of different fungi isolated from soils of different microhabitats of Eastern Himalayan range for mycosynthesis of silver nanoparticles and also studied their efficacy as antimicrobials alone and in combination with commonly used antibiotics against *S. aureus* MTCC96, *Streptococcus pyogenes* MTCC1925, *Salmonella enterica* MTCC735 and *Enterococcus faecalis* MTCC2729. Out of all these isolates *Aspergillus terreus* SP5, *Paecilomyces lilacinus* SF1, and *Fusarium* sp. MP5 were found to synthesize silver nanoparticles. The mycosynthesized nanoparticles showed potent antibacterial activity, and their syngergistic effect with erythromycin, methicillin, chloramphenicol, and ciprofloxacin was significantly higher compared to inhibitions by silver nanoparticles alone. The results obtained by Devi and Joshi [149] showed the resemblance with the findings reported in past few studies on demonstration of syngergistic effect of silver nanoparticles on different bacteria like *E. coli*-JM-103 (ATCC 39403), *S. aureus* (ATCC 25923), and *P. aeruginosa* (MTCC 424) [105, 106], against *K. pneumoniae* (MTCC-7407), and *E. aerogenes* (MTCC-6804) [88] using different commercially available antibiotics like kanamycin, erythromycin, oxacillin, tetracycline, vancomycin, gentamycin, etc.

4.1.2 Antifungal activity

Similar to bacterial resistance, resistance of fungal infections has emerged in recent years and is a major health problem [150]. Silver nanoparticles showed effective antifungal activity. *Candida* species represent one of the most common pathogens resistant to many drugs, which are responsible for fungal infections often causing hospital-acquired sepsis with an associated mortality rate up to 40% [151]. Currently, most of the available effective antifungal agents are based on polyenes, trizoles, or echinocandins. However, administration of these antifungal agents was often accompanied by various complications such as amphotericin B toxicity and adverse effects of some azoles including toxicity and drug interactions and yeast resistance to antifungal therapy [152, 153]. Silver nanoparticles, exhibiting very strong bactericidal activity against both Gram-positive and Gram-negative bacteria, including multiresistant strains, can be considered as potential antifungal agents.

Kim et al. [154] reported that spherical silver nanoparticles showed potent activity against *Trichophyton mentagrophytes*, *Trichophyton beigelii*, and *Candida albicans* compared with that of commercially available antifungal agents (amphotericin B and fluconazole). The antifungal effects of silver nanoparticles and their mode of action were investigated. Silver nanoparticles may exert an antifungal activity by disrupting the structure of the cell membrane and inhibiting the normal budding process due to the destruction of membrane integrity. There was the formation of pits on the membrane surfaces and finally the formation of pores and subsequently cell death. Similar results were also reported by Monteiro et al. [155] against *C. albicans* and *C. glabrata* biofilms. Gajbhiye et al. [156] have evaluated the combined effect of fluconazole and silver nanoparticles for their antifungal activity against *Phoma glomerata*, *P. herbarum*, *F. semitectum*, *Trichoderma* sp., and *C. albicans* by disc diffusion method. The antifungal activity of fluconazole was enhanced against the test fungi in the presence of silver nanoparticles. Fluconazole in combination with silver nanoparticles showed the maximum inhibition against *C. albicans* followed by *P. glomerata* and *Trichoderma* sp., whereas no significant enhancement in activity was found against *P. herbarum* and *F. semitectum*. Apart from these, silver nanoparticle-encapsulated β-cyclodextrin was found to have potential antifungal activity against human opportunistic pathogen like *A. fumigatus*, *Mucor ramosissimus*, and *Chrysosporium* species [157]. Monteiro et al. [158] investigated the potential antifungal activity of silver nanoparticles against *C. albicans* and *C. glabrata* biofilms

in combination with commercially available antifungal agents like nystatin and chlorhexidine digluconate. Similarly, in another study, silver nanoparticles synthesized using *Gracilaria corticata* were used for evaluation of their antifungal activity against *Candida* sp. [159]. Recently, Dar et al. [89] reported the remarkable antifungal activity of silver nanoparticles synthesized from *Cryphonectria* sp. against *C. albicans*, concluding that silver nanoparticles can be used as potential antifungal agents.

4.1.3 Antiviral activity

Sun et al. [160] investigated the antiviral (HIV-1 BaL) activity of silver nanoparticles (10 nm in size) toward post-infected Hut/CCR5 cells. The viral content in the cells were determined by measuring p24 antigen production after 3 days of infection. The silver nanoparticles (0.5, 5, 50 μM) prepared in HEPES buffer showed dose-dependent anti-retrovirus activities, and high potency was exhibited at 50 μM in inhibiting HIV-1 replication. Gold nanoparticles of approximately 10 nm showed relatively lower anti HIV-1 activity (6–20%) when compared to silver nanoparticles (98%). The cytoprotective effect of silver nanoparticles toward HIV-1-infected Hut/CCR5 cells was determined using TUNEL assay after 3 days treatment. The cells treated with silver nanoparticles showed significant reduction in apoptotic cells from 49% to 19% confirming the ability of silver nanoparticles for inhibiting viral replication in Hut/CCR5 cells and, hence, reduce HIV-associated apoptosis. The selective antiviral properties of silver nanoparticles were further confirmed by MTT assay indicating no acute cytotoxicity associated with silver nanoparticles toward Hut/CCR5 cells with more than 80% cell survive at silver nanoparticle concentration of 50 μM.

Rogers et al. [161] demonstrated the antiviral activity of silver nanoparticles against Monkeypox virus plaque formation. Nanoparticles of 10–80 nm and with or without polysaccharide coating or silver nitrate at concentrations of 100, 50, 25, and 12.5 μg/ml were evaluated for efficacy using a plaque reduction assay. Both silver nanoparticles of size 25 nm (polysaccharide coating) and 55 nm (non-coated) exhibited a significant ($p \leq 0.05$) dose-dependent effect of test compound concentration on the mean number of plaque-forming units. Mode of antiviral action against HIV-1 was elucidated by Lara et al. [162]. They have suggested that silver nanoparticles exert anti-HIV activity at an early stage of viral replication, most likely as a virucidal agent or as an inhibitor of viral entry. Silver nanoparticles bind to gp120 (glycoprotein 120) in a manner that prevents CD-4-dependent virion binding, fusion, and infectivity, acting as an effective virucidal agent against cell-free virus and cell-associated virus. Besides this, the silver nanoparticles also inhibit post-entry stage of the HIV-1 life cycle. Xiang et al. [163] also reported the *in vitro* inhibitory effect of nanosilver particles against H1N1 influenza A virus.

An interesting application of silver nanoparticles has been described by Fayaz et al. [164]. They used nanoparticles as a coating for polyurethane condoms. Such nanosilver-coated condoms exerted a highly inhibitory activity against HIV-1, HSV-1, HSV-2, and several bacteria and fungi and can be considered a real broad-spectrum antimicrobial agent against sexual-transmitted diseases causing pathogens. Recently, Gaikwad et al. [165] demonstrated the antiviral effect of silver nanoparticles against viruses like herpes simplex virus types 1 and 2 and with human parainfluenza virus type 3.

5 Wound healing efficacy of silver nanoparticles

Laboratory studies confirm that bacteria and bacterial products, such as endotoxins and metalloproteinase, can cause disturbances in all phases of wound healing. It ultimately resulted in prolonging the debilitation of the patient by slowing wound healing and increasing health care costs. Increased bacterial burden in a wound also affects tissue oxygen availability [166].

Silver-based wound dressings are often used for wound healing, and specific silver products may have a definite positive effect on wound healing and may be used to maintain a microbe free, moist wound healing environment. The number of biochemical effects of silver on the wound has been documented. Besides its antimicrobial activity, silver was proven to have other beneficial effects on the wound bed. Silver-based technologies in particular provide added benefits by downregulating metalloproteinase to levels that facilitate wound healing [167]. Extensive treatment of acute burn wounds with silver sulfadiazine has recently raised concern about potential silver toxicity [168]. The use of silver in the past has been restrained by the need to produce silver as a compound, thereby increasing the potential side effects.

A study suggests that nanocrystalline silver specifically plays an important role in altering or compressing the inflammatory events in wounds and facilitating the early phase of wound healing. These benefits are associated with reduced local matrix metalloproteinase levels and enhanced cellular apoptosis [169]. The ultimate goal

for wound healing is a speedy recovery with minimal scarring and maximal function. As earlier we have described how silver nanoparticles are superior to silver ions, Tian et al. [170] investigated the effect of silver nanoparticles on wound healing and scar tissue formation using thermal injury, diabetic wound, and chronic wound models in mice. Silver nanoparticle-grafted dressing with a silver content of 2.75 mg/ml corresponding to 0.4777 mg of silver nanoparticles on each dressing was used in the study. Dressing coated with 1% silver sulfadiazine cream (3.18 mg/ml) was used as the control group. In the thermal injury model, the animals treated with silver nanoparticles completely healed in 26.5±0.93 days, whereas sulfadiazine group healed in 37.4±3.4 days. The wound treated with silver nanoparticles, after healing, showed the most resemblance to normal skin compared to silver sulfadiazine. Histological evaluation corroborated the gross appearance with the presence of a thin epidermis and nearly normal hair for silver nanoparticles treated group.

Silver nanoparticles synthesized by *A. niger* extracellularly were evaluated for its wound healing activity. For this purpose, excision wound model and thermal wound model were used [171]. In case of excision wound model, faster wound healing took place. In case of animals with different concentrations of silver nanoparticles, complete healing was obtained within 8 days, while control group shows the least rate of wound healing. In case of thermal wound model, ointment of different percentage of silver nanoparticles (5%, 10%, 15%, 20% w/w) was used. Twenty percent (w/w) silver nanoparticle ointment-treated groups showed significant wound healing from fourth day onward, while 10% ointment-treated group showed wound contraction from eighth day onward and achieved 100% with a closer time of 13 days. The control group of animals took 18 days for reepithelization, while the silver nanoparticle group took only about 13 days. It was found that the animal group treated with the silver nanoparticle ointments showed significant reduction in the period of epithelization.

6 Antimicrobial activity of other inorganic nanoparticles

Nanosized metal oxides represent a new class of important materials that are increasingly being developed for its role in research and health-related applications. Highly ionic metal oxides have various physical and chemical properties and also show antimicrobial activity. Inorganic nanocrystalline metal oxides are particularly interesting because they can be prepared with extremely high surface areas and are more suitable for biological application. The advantages of inorganic antibacterial materials over organic antibacterial materials are that the former show superior durability, less toxicity, and greater selectivity and heat resistance. Iron oxide has been widely used in biomedical research because of its biocompatibility and magnetic properties [172, 173]. Nanoparticles of iron oxide, with size <100 nm, have been developed as contrast agent for magnetic resonance imaging (MRI) [174], as hyperthermia agents [175], and as a carrier for targeted drug delivery to treat several types of cancer [176, 177]. Lee et al. [178] reported that the inactivation of *E. coli* by zero valent iron nanoparticles was due to the penetration of the small particles into *E. coli* membranes. Nanoparticles could then react with intracellular oxygen, leading to oxidative stress, and eventually causing disruption of cell membranes.

Tran et al. [179] evaluated the bactericidal effect of iron oxide nanoparticles against *S. aureus*. These iron oxide nanoparticles were synthesized by a novel matrix-mediated method using polyvinyl alcohol (PVA). The mechanism behind the antimicrobial activity was hypothesized that reactive oxygen species (ROS) were generated by iron oxide nanoparticles, which could kill bacteria without harming nonbacterial cells. In practice, Gram-negative and Gram-positive bacteria as well as fungi could exist in the polluted water. Diao and Yao [180] had investigated the inactivation effect of nanoscale iron nanoparticles on Gram-negative *Pseudomonas fluorescens* and Gram-positive *B. subtilis* bacteria as well as *Aspergillus versicolor* fungus with different concentrations, which were mostly found in polluted water. The result obtained confirmed that *B. subtilis* was completely inactivated when mixed with 10 mg/ml of nanoparticles in aerobic condition, while survival rate increased when the concentration of nanoparticles decreased. The same result was obtained in case of *P. fluorescens*. None of the iron suspension tested had significant inactivation effect on *A. versicolor*. Babushkina et al. [181] studied the antibacterial action of iron nanoparticles on 10 strains of *S. aureus* isolated from a patient with purulent complications. They proved that the antibacterial effect of nanoparticles depend on the nanoparticles' form, their concentration, and time of action. Concentration of 0.1 mg/ml and 1 mg/ml of iron nanoparticles has provoked the decrease in quantity of microbial cell from 3% to 34%.

Zinc oxide (ZnO) nanoparticles have shown significant antibacterial effect on *S. aureus*. For a long time, ZnO powder has been the main constituent for the preparations used for dermatological applications in creams, lotions, and ointments on account of its antibacterial properties

[182]. However, nanoparticles of ZnO were much more effective agents in controlling the growth of various microorganisms, and the smaller the particle size, the greater was the efficacy in inhibiting the growth of bacteria. Jones et al. [183] showed the antimicrobial activity of zinc oxide nanoparticles, which was size dependent in the presence of normal visible light. Different bacteria such as Gram-positive *S. aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *B. subtilis*, and Gram-negative *E. coli* were tested against different metal oxide nanoparticles such as MgO, TiO_2, Al_2O_3, CuO, CeO_2, and ZnO. Padmavathy and Vijayaraghavan [184] investigated the antibacterial activity of ZnO nanoparticles with various particle sizes; *E. coli*, a Gram-negative bacterium, was selected as the target organism. Antibacterial activity of these nanomaterials was measured by disc diffusion method. The results showed the size-dependent activity. Similarly, Liu et al. [10] showed that the inhibitory effect of ZnO nanoparticles on the growth of *E. coli* increases with the increase in the concentration of nanoparticles.

Like silver nanoparticles, copper nanoparticles also showed the size-dependent antimicrobial activity. Recently, Azam et al. [185] studied the effect of different sizes of copper oxide nanoparticles on Gram-negative and Gram-positive bacteria (viz. *E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. aureus*). They found that the small-sized nanoparticles (20±1.24 nm) showed high antibacterial potential compared to large-sized nanoparticles (28.9±1.22 nm). From these findings, it can be concluded that to achieve the maximum antibacterial activity, we have to develop methods for the synthesis of monodisperse copper nanoparticles having small size. The antimicrobial activity of the copper nanoparticles was tested against four pathogenic bacteria such as *Salmonella*, *Shigella*, and *Pseudomonas* species at different concentrations [186]. Copper nanoparticles have expressed greater inhibitory effect on growth of clinical strains of *Staphylococcus* than iron nanoparticles [181]. Ramyadevi and group [187] also studied the antifungal activity of copper nanoparticles against some fungi like *Aspergillus flavus*, *A. niger*, and *C. albicans*. The maximum activity was reported against *C. albicans*, while minimum activity was observed against *A. flavus*. Moreover, during evaluation of antimicrobial activity of copper nanoparticles, it was found that nanoparticles showed more inhibitory activity in bacteria than the fungi.

Matsunaga and group [188] reported for the first time the microbiocidal activity of TiO_2 nanoparticles. Reactive oxygen species generated on irradiated TiO_2 surfaces have been shown to operate in concert to attack polyunsaturated phospholipids in bacteria [189] and to catalyze site-specific DNA damage by generating H_2O_2 [190], which result in subsequent cell death. TiO_2-mediated photoxidation have emerged as a promising technology for the elimination of microorganisms in many applications [191]. The mechanism behind the bactericidal activity of TiO_2 was explained as oxidative damage first took place on the cell wall when the TiO_2 made contact with the cell. As photocatalytic action progressed, the cell permeability increases. TiO_2 particles have easier access and cause photoxidation of intracellular components thereby accelerating cell death [192].

Desai and Kowshik [193] synthesized sunlight responsive TiO_2 nanoparticles by simple sol gel method. The antibacterial activity of these TiO_2 nanoparticles was tested against four human pathogens *E. coli*, *P. aeruginosa*, *K. pneumoniae*, and *S. aureus*. The bactericidal activity was determined by adding 0.1 M TiO_2 to the bacterial cell suspension and exposing them to sunlight. The samples were withdrawn at regular time intervals, and the numbers of surviving cells were determined by viable count method. The order of susceptibility of the organisms to inactivation by TiO_2 was found to be *S. aureus*>*K. pneumoniae*>*P. aeruginosa*>*E. coli*.

7 Silver nanoparticles: application in fabrics, cosmetics, and agriculture

The Silver Nanotechnology Commercial Inventory (SNCI) added new categories, which focus the implications of silver nanoparticle usage [194]. The SNCI examined silver nanoparticle applications that are available on the market or have the potential to contact or affect the public directly or indirectly. The inventory includes products such as silver nanoparticles or are associated with a precursor products, which included consumer products, medical applications, and precursor (synthetic silver nanoparticles) products that will be incorporated into final products (e.g., antibacterial, deodorants, cosmetics, or fabrics). Silver nanoparticle technologies appear in a variety of manufacturing processes and end products as coating, which is applied to the product by the manufacturer; some products are in a liquid form such as a homeopathy colloid or contained within a shampoo and are meant to be applied to form a coating and spray. It can also be embedded in a solid such as a polymer master batch or be suspended in a bar of soap. Silver nanoparticle can also be utilized in the textile industry by incorporating it

into the fiber (spun) or produced as a powder. The total number of commercial product records in the inventory was 240, in which 214 were general commercial products and 26 precursor products from 65 companies involved in the design and manufacturing of the commercial products listed from China, Germany, Iran, Japan, New Zealand, Singapore, Korea, Taiwan, Thailand, the United Kingdom, and the United States of America [194]. The distribution of commercial products is displayed in Table 1.

The commercial products were categorized under a scheme similar to the Project on Emerging Nanotechnologies Consumer Product Inventory [195]; however, two additional categories were added as medical applications (e.g., antibacterial, healing, etc.) and public. The latter one includes products that the public would like to have contact with, but an individual would not necessary buy [194] (Table 2). The Health and Fitness markets are seeing the biggest emergence of products utilizing silver nanoparticles (155 records) compared to other categories such as appliances (15), medical applications (10), and electronics and computers (8). Health and Fitness includes subcategories such as personal care (71), sporting goods (11), clothing (56), and cosmetics (17%) with no records under filtration or sunscreen applications. Personal Care includes a real personal care (51), clothing (13), home/garden (cleaning) (2), food/beverage (supplement) (2), and cosmetics (1). The work also displayed the availability of data (from SNCI) recovered for each data field [194] (Table 3).

It is clear from the market imposition that the "Recommended Uses" field and "Application of Nanotechnology" contained the highest percentage (98% and 93%, respectively) of available data as there are a necessity of incentive the customers to recognize the product and to associate with innovative technology. Approximately 88% of the products listed claimed some form of antibacterial or antimicrobial protection. The strategy in this areas was related to the relationship of antimicrobial and antibacterial with words such as harmful, repelling, kill, disinfectant, antibiotic, suppression and other terms that induce the customers to think in the reduction of microbial life. However, an important information is rate of silver release that is considered one of the major factors in determining how toxic a product is to bacteria. Only one US Company, Natural Immunogenic Corp. and their product Sovereing Silver™, has information on the rate in which silver is being released [196].

Table 1 Distribution of commercial products by nanomaterial [194].

Materials	General commercial products	Precursor products
Coating	59	7
Coating/spray	10	0
Powder	3	4
Solid	36	5
Liquid	50	6
Spun	13	3
N/A	43	1

Table 2 Distribution of product categories [194].

Product category	Number of records	Product category	Number of records
Appliances	15	Automotive	0
Cross-cutting	23	Electronics and computer	8
		Goods and children	5
Food and beverages	25	Home and garden	26
Health and Fitness	155	Public	6
Medical applications	10		

Table 3 Available information represented in the inventory [(percentage of products with/without information (%)] [194].

Data field	Percentage of data represented in the inventory	
	Data available (%)	Data unavailable (%)
Product testing	37	63
Antibacterial claims	88	12
Recommended uses	98	2
Application of nanotechnology	93	7
Synthesis	13	87
Structure	55	45
Expected lifetime	39	61
Concentration	16	84
Size	45	55
Number of dispersive product	31	69

7.1 Application of silver nanoparticles in fabrics

Infection is a well-recognized complication of implantable devices for which a wide variety is now in use. Rai et al. [197] reviewed that among the different antimicrobial agents, silver has been most extensively studied and used since ancient times to fight infections and prevent spoilage. The antibacterial, antifungal and antiviral properties

of silver ions, silver compounds and silver nanoparticles have been extensively studied. Silver is also found to be non toxic to humans in minute concentration. Therefore, such silver nanoparticles can be used as new generation antimicrobials.

An essential event in initiation of infection is microbial adhesion to the devices. Once adhesion has occurred, proliferation leads to the development of a biofilm which is not susceptible to most therapeutic agents. An alternative to reducing bacterial adhesion on medical devices is to focus on materials that release antimicrobial agents. True impregnation of polymer with antimicrobials has led to only one clinical application, but this has demonstrated the superiority of impregnation over coating [198]. The antimicrobial properties of silver are related to its oxidized form, a form of silver that is not necessarily present at the surface coated with metallic silver. Polymers that release silver in the oxidized form have shown strong antimicrobial activity and would act as reservoir of silver and be capable of releasing silver ion for extended periods. Biomaterials coated with silver oxide or alloys have all been used to reduce infection but they proved to be disappointing in clinical trials. Extensive reviews in this area were recently published [199–201]. Possible reason for their failure would have been the inactivation of the silver coating by blood plasma and the lack of prolong activity. Coating that incorporate agents with direct antibacterial activity was effective at reducing bacterial adhesion *in vitro* and, in some cases, lessening the effects of implant-associated infection *in vivo* [202].

Furno et al. [203] demonstrated the use of silver nanoparticles in impregnation of medical devices to increase their antimicrobial efficacy against infectious pathogens. They have introduced silver into silicon elastometer, showed the result in distribution of nanoparticles of metallic silver throughout the polymer, and was the only method known to impregnate the polymer with silver. Silicon discs of 0.45 mm were impregnated with silver nanoparticles. *S. epidermidis* was used as the test bacterium, which was found to be most susceptible. Impregnated silver nanoparticles could continuously release silver ions and, hence, shows antimicrobial activity. Impregnation of such antimicrobial agent into medical devices such as surgical utensils masks, bedsheets, cover, etc., may help to reduce the chances of postoperation complications, which are the major reason of death of the patient, and it also protects the inner and outer surfaces of medical devices against bacterial colonization [204].

As the major problem of supporting the silver nanoparticles in the fabrics, different methods have been used for surface modifications of textiles. Yuranova et al. [205] have deposited nanoparticles from their metallic salt solution on the surface pretreated with radio frequency (RF)-plasma and vacuum-UV. Sol gel processing loading nanoparticles into liposomes [206] uses nanoporous structure of cellulose fiber as a nano-reactor for *in situ* synthesis of metal nano-particles. Potiyaraj et al. [207] have designed a process to grow silver nanoparticles via successive treatment of $AgNO_3$ and AgCl. Perkas et al. [208] have incorporated nanoparticles into the PA66 chips via the reduction of $AgNO_3$ solution using ultrasound irradiation under Ar purge. Jiang et al. [209, 210] used chemical pleating for functionalization of fabrics with nano-particles. Gorensek and Recelj [211] have used a jet dyeing machine to exhaust nanoparticles. Perelshtein et al. [212] have reduced the silver ions to metallic silver on the fabrics under sonication and called sonochemical coating. Jiang et al. [213] prepared plasma aldehyde functional surfaces with the reduction ability of the silver ion to Ag nanoparticles. Polyelectrolyte self-assembled multilayers have been designed on the basis of interaction between oppositely charged sequential layers via layer-by-layer coatings. Functionalization resin with metallic ion via ion exchange and then reduction of ion embedded in the matrix to the nanoparticles has been presented by Maria et al. [214].

Vigneshwaran et al. [215] reported a novel *in situ* synthesis protocol for silver nanoparticles onto cotton fabrics in which the cotton fabric immersed in silver nitrate solution was autoclaved for 15 min (at this condition the terminal aldehyde residue from starch at the cotton fabric reduced the silver nitrate to silver metal) leading to stabilization of the nanoparticles on fabric. Besides the excellent antibacterial activity, the silver nanoparticles impregnated fabrics expressed significant UV-protection capability in comparison with the untreated fabrics. Ilic et al. [216] in an untreated and air radio frequency plasma-treated polyester fabrics loaded with silver nanoparticles exhibited excellent antibacterial activity against Gram-negative bacterium *E. coli* and Gram-positive bacterium *S. aureus*. Plasma-pretreated polyester fabrics preserved excellent antibacterial activity even after five washing cycles (a loss of 40% of silver was observed). Released silver from the washing effluent was efficiently removed (90% in 3 h) by recycled wool-based nonwoven sorbent modified with hydrogen peroxide and biopolymer alginate.

Jiang et al. [213] reported that nanostructured silver surfaces of polyester fibers are possible to fabricate via a sputtering method. In comparison with untreated polyester, the average ultraviolet protection factor (UPF) of the silver-coated polyester increases significantly. The results confirmed that silver-coated polyester offers

excellent protection from UV radiation. After modification with nanostructured silver, the properties of the surfaces of the polyester change from hydrophilic to hydrophobic, and the silver-coated polyester possesses excellent antibacterial performance. Such silver-coated fabric could therefore be used in UV shielding, hydrophobic coating, and antibacterial applications. Raja et al. [217] synthesized silver nanoparticle-polyvinyl pyrrolidone (PVP) composite in powder form for textile applications, using sonochemistry method comprising sonication and reduction with trisodium citrate followed by spray drying. The silver nanopowder has been applied on cotton and wool to impart antimicrobial efficacy by exhaustion method.

However, in general, conventional surface modification of textiles with inorganic nanoparticles is not permanent especially against washing, and several steps are necessary to fix the silver nanoparticles to the fabrics with a high cost, non-ecological and time-consuming processes. In order to avoid free radical formations and thermal stability of these materials for medical usages of antimicrobial textiles, a new method for the stabilization of nanostructures on the textile surfaces was described [218]. This technique was the embedding of silver nanoparticles in a cross-linkable polysiloxane layer in combination with or after nano-finishing process with high stability against, e.g., oxygen radicals and biocompatible and resistant to domestic laundering and dry cleaning as well as water and fire retardancy and anti-pilling [219]. Besides this method, a soft one, easy to apply in the industry, was the biogenic silver nanoparticles in fabrics. Durán et al. [220] studied the impregnation of biogenic silver nanoparticles in cotton and polyester fabrics. The nanoparticles were produced by *F. oxysporum*, and silver nanoparticles impregnated in the fabrics by a padding method were obtained. These fabrics exhibited high antibacterial effects against *S. aureus*. In another study, the impregnation of cotton and polyester fabrics with biogenic silver nanoparticles from *F. oxysporum* was carried out by two different methods: padding and centrifugation. The results showed different homogeneity in the silver nanoparticle distributions in the fabrics, both methods being adequate for impregnation [221]. Duran et al. [222] studied the bioremediation process of biogenic silver nanoparticles released from fabrics in the washing process. This treatment was based on biosorption, which was very efficient for the elimination of silver nanoparticles remaining in the wash water. The process also allowed the recovery of silver material that was leached into the effluent for reutilization, avoiding any effect to the eco-environment. This was the first bioremediation process related to production of fabrics and the subsequent washing process. Silver nanoparticles from biomass filtrate of *F. solani* in a finishing formulation were prepared and applied to cotton fabrics with and without binder. The efficiency and durability of the silver nanoparticle-based antibacterial finish were determined. The finish appears as deposits on the surface of the fibrils/fiber of the treated cotton. Efficiency of the antibacterial finish on the cotton fabric, expressed as bacterial reduction, was high. These values were reduced to around 50% upon exposing to laundering for 20 cycles. This problem was overcome by incorporation of a binder (Printofix Binder MTB EG liq.) in the finishing formulation: under this condition, antibacterial cotton fabrics have bacterial reduction of 94% and 85% after 20 washing cycles could be prepared [223]. Recently, Patra and Gouda [224] reviewed the applications of nanotechnology in textile industry. According to them, application of nanotechnology economically extends the properties and values of textile processing and products. The use of nanotechnology allows textiles to become multifunctional and produce fabrics with special functions, including antibacterial, UV protection, easy to clean, water and stain repellent, and anti-odor.

7.2 Application of silver nanoparticles in cosmetics

The antimicrobial effect of silver nanoparticles is widely known in the literature; however, the silver nanoparticles have some limitations as a preservative as, in potential, they could interact with many biological systems. In a very recent study, the action on microorganisms, the permeability of chemically synthesized silver nanoparticles in human skin and cytotoxicity in human keratinocytes under ultraviolet B irradiation were studied. Silver nanoparticles were found to be very stable, and no sedimentation was observed during a year, and no penetration in human skin or ultraviolet-enhanced cell death was also not observed (better preservative than methylparaben). The authors suggested that silver nanoparticles may have potential for use as a preservative in cosmetics [225]. Many of the precursor products, as described above, that are being developed are marketed for a specific group of applications. This is particularly apparent in the development of silver nanoparticles coatings. The nanocosmetics, NANOVER™, made by a Korean company called Nanogist Co., Ltd. demonstrated this versatility. They offer an intermediary in different types of colloids composed of silver nanoparticles-titanium-dioxide with an average particle size of 5 nm (Figure 1).

Figure 1 Silver nanoparticles products modified from Nanover-Nanogist.

8 Application of silver nanoparticles in agriculture

8.1 Food

The Woodrow Wilson International Center for Scholars published a review dealing with both the applications and regulatory (and toxicological) issues related to nanoparticles incorporated in food packaging materials [226, 227]. One of these nanoparticles was silver nanoparticles that were incorporated to increase the barrier properties of packaging materials. One concern was the nanoparticle migration; however, the migration of metals from biodegradable starch/clay nanocomposite films used in packaging materials (vegetable samples) was shown to be insignificant [228]. Of course, more studies are needed to reach a conclusive statement on this issue. Nanoparticles can also be applied as reactive particles in packaging materials. The use of active packaging releasing silver nanoparticles with antimicrobial functions into the food will lead to direct consumer exposure to free nanoparticles. Then, the product must give information on the effects of these nanoparticles to human health following chronic exposure. The most important information should be if the silver nanoparticles are really free and how many of these particles are released to the food. Moreover, attention should be paid to life cycle analysis (LCA) and effects on the environment [229]. Improving the risk analyses of the application of food nanotechnology is needed to have more information in the availability of different types of food products containing nanomaterials. The actual strategy for these information are the database of consumer products of the Nanotechnology Project (www.nanotechproject.org) of the Woodrow Wilson International Center for Scholars, the Global New Products Database of Mintel (www.gnpd.com), the Nanotechnology Product Directory (www.nanoshop.com), and the report of nanoforum (Nanotechnology in agriculture and food; www.nanoforum.org). The survey clearly demonstrated that nanotechnology in the agro-food production chain are claimed to be applied throughout all phases of food production [229].

In the case of silver nanoparticles, the production and processing of food, conservation and also as food additive/supplement, packaging materials/storage, food preparation devices, refrigerators, storage, containers, water purification/soil cleaning, and antibacterial sprays are summarized in Table 4. Some applications of silver nanoparticles are as nutritional supplements [230]: Nanoceuticals TM Silver 22 (RBC Life Science® Inc., USA), Sovereing SilverTM (Natural-Immunogenic Corporation, USA), Advanced Colloidal Silver (Utopia Silver Supplements, USA). Rashidi and Khosravi-Darani [231] reviewed that nanotechnology

Table 4 Summary of applications of nanotechnology in the food production chain.

Chain phase/type of nanoparticles	Application	Nanotechnology	Function	Like-hood of free nanoparticles available to the consumer
Production and processing of food	Refrigerators, storage container, food preparation equipment	Incorporated nanosized mostly silver	Antibacterial coating	-/+
Conservation metals nanoparticles (specially silver)	Food products Food additive/supplement packaging materials/storage food preparation devices, refrigerators, storage containers water purification/soil cleaning sprays	Nanosized silver spray	Antibacterial action claimed enhanced gastrointestinal uptake of metals increase barrier properties clean surface antibacterial coating removal/ catalyzation/ oxidation of contaminants antibacterial	+/+

Note: Modified from Bouwmeester et al. [229]. (b) Legend: "-/+", contact with food product during production, but no direct consumer exposure to NPs is expected; "++", NPs directly added to consumer products.

has the potential of application in the food industry and processing. The application of nanotechnology in food systems will provide new methods to improve safety and the nutritional value of food products. Natural antimicrobial action of silver has been utilized in a number of active food contact materials (FCMs) claimed to preserve the food materials within longer by inhibiting the growth of microorganisms (see some examples) [232] (Figure 2).

Figure 2 Nano-silver airtight plastic food container.

8.2 Plant growth

Bacterial contamination is a severe problem in plant tissue culture techniques. The potential of silver nanoparticles for the removal of bacterial contamination in nodal explant of *Valeriana officinalis* L. was evaluated. Results showed that using 100 mg/l of silver nanoparticles solution after surface sterilization resulted in the highest percentage of disinfected explants [233]. The traditional propagation methods of olive trees are complicated mainly by the contamination in the propagation steps. Recently, a previous surface sterilization of the surface of olive explants with 10% Clorox for 10 min after 70% ethanol for 1 min may be used. Silver nanoparticles (4 mg/l) used as supplementary disinfectant treatments and microcuttings after adding to the media were found to be fully effective to control explant internal contaminations, and no harmful effects were observed on explants and their growth [234]. Similarly, Rai and Ingle [235] reviewed the role of nanotechnology in agriculture with special reference to management of insect-pest. Further, they also explained the possible role of nanotechnology in precision farming and development of nanobased pesticides and insecticides.

9 Nanotoxicity: an emerging problem

Even though there is vast progress in research in the field of nanotechnology, relatively little knowledge is available about the consequent health effects of exposure to nanoparticles. This is going to be a serious problem. Many research efforts are in progress throughout the world to characterize the risks of exposures to nanoparticles. The workers, their family members, and consumers of products utilizing nanoproducts are getting exposed [236]. The exposure was probably occurring through inhalation, ingestion [237, 238], and thorough skin [239]. These materials may also present an environmental risk. A recent study on the biological effects of nanomaterials has showed that some of the manufactured nanoparticles do exhibit unexpected toxicity to living organisms. Thus, there is continuing fear regarding the toxicity of nanoparticles with sizes <100 nm compared to larger particles of the same substance. On the contrary, no current specific medical evaluation protocols exist for exposure to nanoparticles, which is a real menace of nanoparticles, causing severe problem in the form of toxicity are discussed as follows.

Asbestos (crocidolite) is a human carcinogen that exclusively induces malignant mesothelioma [240]. Cytogenotoxic effects of crocidolite in a human mesothelioma cell line, MSTO211H, and a human promyelocytic leukemia cell line, HL60, was reported [241]. It was previously known that the MSTO211H cells had phagocytotic activity, whereas the HL60 cells did not. Findings of Takeuchi and group indicated that MSTO211H cells were susceptible to the cytogenotoxic effects of asbestos due to their phagocytotic activity.

Christie et al. [242] have investigated the effect of water-soluble fullerene aggregates, nano-C_{60}, on HDF, HepG2, and NHA cells in culture. They have determined that lipid peroxidation and resulting membrane damage were responsible for the cytotoxicity of nano-C_{60}. Further, it was also observed that the oxidative damage and toxicity of nano-C_{60} were prevented by addition of L-ascorbic acid to the culture medium as an antioxidant. The electron microscopy of fullerene (C_{60})-exposed *Chironomus riparius* shows its aggregates in the gut and causes damage to the microvilli, thereby, affecting the normal larval growth and altered morphological changes [243]. The effect of carbon black (CB) nanoparticles with mean aerodynamic diameters of 14, 56, and 95 nm were observed by Koike and Kobayashi [244]. It shows that CB nanoparticles can induce oxidative stress in alveolar epithelial cell, which is to, some extent, mediated by surface function of particles [244]. Inhalation of diesel engine-derived nanoparticles is also found to have cytotoxicity [245]. This nanoparticle inhalation intensifies neutrophil infiltration in the lung, which is induced by LPS in a concentration-dependent manner.

Kidney, liver, and spleen were found to be target organ for copper nanoparticles. Copper nanoparticles having average size of 23.5 nm were found to induce pathological changes and grave injuries on kidney, liver, and spleen in mice [246]. While, Meng et al. [247] have proposed that the ultrahigh chemical reactivity of nanocopper results in the specific nanotoxicity. Using chemical kinetics study *in vitro* and blood gas and plasma electrolytes analysis *in vivo*, copper nanoparticles were found to cause huge toxicological difference between small size (23.5 nm) and big size (17 μm) particles. A latest study showed that copper oxide nanoparticle (CuONP) induces autophagy in MCF-7, a breast cancer cell line. This result might be a cellular defense mechanism resulting due to CuONP-mediated toxicity [248]. Zinc oxide (ZnO) NPs are used in a variety of different applications including food additives, cosmetics, textiles, plastics, paints, as drug carriers, and fillings in medical materials [249, 250]. It is known that ZnO nanoparticles are soluble in water and have antimicrobial properties. Additionally, it is considered as very toxic to aquatic organisms and as an environmental hazard. Bai et al. [251] have revealed that nano-ZnO (30 nm) killed zebrafish embryos by retarding the embryo hatching, reducing the body length of larvae and causing tail malformation. Furthermore, researchers at Shanghai University, China, have revealed that zinc oxide nanoparticles can harm or destroy stem cells in the brain of mice [252].

Similarly, iron oxide nanoparticles were found to cause cell death associated with membrane damage, while single-walled carbon nanotube induces oxidative stress followed by apoptosis. Cerium oxide nanoparticles of different sizes (15, 25, 30, 45 nm) at the concentration of 5, 10, 20, 40 μg/ml lead to cell death, ROS increase, GSH decrease, and the inductions of oxidative stress-related genes hemeoxygenase-1, catalase, glutathione S-transferase, and thioredoxin reductase, and finally exerted cytotoxicity by an apoptotic process [253]. The cytotoxicity of 15 nm and 46 nm silica nanoparticles was investigated on human broncho-alveolar carcinoma-derived cells. It was found to reduce cell viability at 10–100 μg/ml of dosage [254]. Titanium dioxide (TiO_2) nanoparticles have been considered as nontoxic, a mineral particle used in the fields like cosmetics, food, and drug. At nanometer scale, they are widely used in industrial products, pharmaceuticals, and cosmetics, e.g., in sunscreens, to efficiently

protect the skin from UV-B radiation [255]. It is also being used as a photocatalyst in environment and wastewater disinfection [256], as a photosensitizer for the photodynamic therapy of human colon carcinoma cells [257]. For this reason, there are increasing chances of TiO_2 exposure to humans at toxic level. In this respect, Wu et al. [258] have investigated the penetration and potential toxicity of TiO_2 nanoparticles following its dermal exposure *in vitro* and *in vivo*. They found that after exposure to isolated porcine skin *in vitro* for 24 h, titanium dioxide nanoparticles of various sizes cannot penetrate through stratum corneum. On the other hand, quite different results were obtained *in vivo*. Following topical application on pig ear for 30 days, TiO_2 nanomaterials of the size 4 nm and 60 nm were found to penetrate through the horny layer of the skin, which can be located in deep layer of epidermis.

Gold nanoparticles (AuNP) of the size 3–8 nm are noncytotoxic, nonimmunogenic in macrophage cells [259]. Nevertheless, a recent study using 20 nm AuNP on embryonic lung fibroblasts confirmed the significant oxidative DNA damage in the form of 8-hydroxydoxyguanosine (8OHdG) adducts, at concentrations as low as 25 mg/ml AuNP. It, therefore, came into sight that regardless of the inert nature of gold, AuNPs are capable of inducing DNA damage through an oxidative stress response, in a cell type, in a size-dependent manner.

Similarly, silver nanoparticles showed different physical characteristics at nanoscale compared to their larger counterparts. At nanoscale, they were more effective inducers of apoptosis and inflammation, which is revealed by phenotypical changes in the liver [260]. Hussain et al. [261] have demonstrated that AgNPs (15, 30 nm) exposure results in concentration-dependent increase in leakage of long form of LDH and showed considerable cytotoxicity at 10–50 μg/ml. While Carlson et al. [262] have studied size-dependent cellular interaction of hydrocarbon-coated silver nanoparticles and found that both Ag (15 nm) and Ag (30 nm) appeared to be toxic at low concentrations (5 and ~10 μg/ml) compared to Ag (55 nm) nanoparticles. A similar conclusion was made by the study of AgNP exposure on MC3T3-E1 and PC12 cell lines [263]. After exposure, AgNPs get internalized and causes acute cytotoxicity and depolarization of the mitochondrial membrane potential. Moreover, it also significantly reduces the total intracellular glutathione level with induction of stress-responsive genes [264]. As per the earlier reports, toxicity of AgNPs depends upon particle size, shape, and capping agent, whereas El-Badaw et al. [265] suggested that their toxicity also depends on their surface. All these findings, therefore, present an outlook for toxicologists, nanotechnologists, industrial members, and governmental regulatory agencies to cooperate, discuss their views, and develop safe nanotechnology.

10 Future perspectives

According to the prediction of the American National Science Foundation, the amount of nanotechnology goods and services market will spectacularly increase in the coming 10–15 years. Particularly, pharmaceutical applications will cover around 180 billion dollar market, which will be made on the basis of new technology. It is also estimated that the use of nanotechnology in the area of public health will improve life quality and increase of the life span, which indicates that nanomedicine will also play a crucial role in the future. In the next few years, research on nanomedicine in drug-delivery systems will lead to breakthrough that facilitates their therapeutic application. The nanomedicine may avoid the adverse effects of traditional therapy for the dreadful diseases like cancer, AIDS, and will improve these therapies by reducing their dose. Within the next 5–10 years, we should see the first commercial nanomedicine accessible to patients, giving them opportunity to use them against conventional formulations. Therefore, the application would begin in hospitals but would eventually reach our homes and working environment.

The potential of nanomedicine also includes the development of nanoparticles as an antimicrobial agent. For example, metallic silver in the form of silver nanoparticles has made a remarkable comeback as a potential antimicrobial agent [76]. Different types of nanoparticles have emerged up with diverse medical applications ranging from silver-based dressings; silver-coated medicinal devices, such as nanogels, nanolotions, etc. But until now, the exact mechanism of action of those nanoparticles is still unknown. Therefore, there is a huge scope in the future to find out the exact mechanism of action of the different nanoparticles on the various biological systems. As discussed above, there is a huge potential for such nanoparticles in enhancing the efficacy of various small and large molecules once the potential growth and limitations of nanoparticle systems are fully understood. Beside promising perspectives of nanotechnology, the assessment of environmental impact of nanoparticles on humans and animals is the urgent need of the hour. It would be useful to establish the degree of environmental mobility and bioavailability of nanoparticles. These factors will decide up to what extension the nanoparticles can be taken up and cause

harm to various organisms including plants. This is a prerequisite for ecological damage as well as effects on public health through entry into drinking water and the human food chain. Therefore, the new methods for the evaluation of nanotoxicity are to be developed. Besides this, the preventive measures to reduce the toxic effects of all nanoparticles are needed.

11 Conclusion

Nanotechnology is the emerging field of science that implies the capacity to work with materials at a nanometer scale. Until now, a vast variety of nanomaterials have been synthesized ranging from nanotubes, nanowires, nano-films, and nanoparticles. Advances are occurring in synthesis of nanostructures, thus, creating novel materials with designed properties. They are synthesized not just by changing the composition of the components, but by controlling the size and shape of the components. The manufactured nanoparticles are important among the different types of nanomaterials. They have unique properties due to a very high surface-to-volume ratio, reactivity, shape, etc. This property is utilized in areas where high surface areas are critical for success.

Hypothetically, nanoparticles can be produced from almost any chemical. But most of the presently used nanoparticles have been made from transition metals, silicon, carbon, and metal oxides consisting of zinc dioxide and titanium dioxide, etc. Many methods for synthesis of nanoparticles are available today, which are specifically categorized under physical, chemical, and biological methods. The physical method for synthesis comprises grinding, arc discharge, laser ablation, etc. Principally, the chemical methods of synthesis require the reduction of metal ion by certain reducing agents. On the other hand, biological methods of synthesis include the use of bacteria, actinomycetes, plants, and fungi. Biological method of synthesis has the edge compared to chemical and physical methods. This is because the biologically synthesized nanoparticles are more biocompatible. Second, there is no need to functionalize the nanoparticles through capping as synthesized nanoparticles itself gets functionalized during its synthesis and is eco-friendly.

These nanoparticles have potential applications in a wide range of area and deserve the most attention in biomedical science compared to progress in other new trends. In biomedical sector most importantly, it will play a crucial role in diagnostics, drug delivery, cosmetics, agriculture, band aids, etc. It has also been used in remediation through pollution absorption, water filtering, disinfection, etc. The best example is the use of inorganic nanoparticles as antimicrobial agents. Silver nanoparticles are exploited as new generation antimicrobials. Owing to its significant activity against many types of pathogens including multidrug-resistant organisms. As the range of nanoparticle types and applications are increasing, their potential toxicities and the properties forcing such toxic responses must also be understood. Undoubtedly, a detailed evaluation of the aspects that influence the biocompatibility and/or toxicity of nanoparticles are vital for the safety and sustainable development of the emerging nanotechnologies. This is because a large number of reported studies gave some insights regarding cytotoxicity induced by several nanomaterials. However, the existing toxicology literature lacks much of the characterization information that allows toxicologists and regulators to assess potential hazards. To cope with the problem of toxicity, the toxicologists need to know the characteristics of the particle that interacts with the biological system and thereby leading to evaluation of all these materials for their potential hazards. Therefore, as new nanomaterials are developed and commercialized, risk associated with them needs to be evaluated for its safer use. With anticipation, these all efforts will permit nanotechnology to develop reliably with a full admiration of their health and environmental impacts. Hopefully, current and future research efforts will eventually result in this concept moving from the bench to the bedside.

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