MINI-REVIEW

Broad-spectrum bioactivities of silver nanoparticles: the emerging trends and future prospects

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Abstract There are alarming reports of growing microbial resistance to all classes of antimicrobial agents used against different infections. Also the existing classes of anticancer drugs used against different tumours warrant the urgent search for more effective alternative agents for treatment. Broad-spectrum bioactivities of silver nanoparticles indicate their potential to solve many microbial resistance problems up to a certain extent. The antibacterial, antifungal, antiviral, antiprotozoal, acaricidal, larvicidal, lousicidal and anticancer activities of silver nanoparticles have recently attracted the attention of scientists all over the world. The aim of the present review is to discuss broad-spectrum multifunctional activities of silver nanoparticles and stress their therapeutic potential as smart nanomedicine. Much emphasis has been dedicated to the antimicrobial and anticancer potential of silver nanoparticles showing their promising characteristics for treatment, prophylaxis and control of infections, as well as for diagnosis and treatment of different cancer types.

Introduction

Multi-drug resistance is a growing problem in the treatment of infectious diseases. The extensive use of broad-spectrum antibiotics has led to resistance to classical antimicrobial agents for many bacterial human pathogens and has posed a major threat to the global health care. The problem of resistance emergence, perfectly depicted by the prevalence of more than 25 % among invasive staphylococcal isolates (methicillin resistant *Staphylococcus aureus*) in some countries (Johnson 2011), is not an exclusive prerogative of bacteria, in fact other noxious human pathogens are actually almost deprived of an efficient drug for their control. Resistance to the commonly used antimalarial drug chloroquine among *Plasmodium falciparum* has also reached nearly 25 % resistance (Fall et al. 2013), emergence of fluconazole-resistant *Candida albicans* strains and intrinsically resistant species including *Candida glabrata* and *Candida krusei* progressively reduce efficacy of the most popular antimycotic fluconazole, and emergence of resistant viral strains, particularly of HIV, creates great problems in anti-retroviral therapy (Johnson et al. 2013). The similar situation has recently been observed for

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insect vectors able to spread several infections: ticks, mosquitoes and lice demonstrated resistance to available anti-arthropod agents (Jayaseelan et al. 2012). Thus, there is an urgent need to search for new alternatives for the treatment and control of infectious diseases, and silver nanoparticles (AgNPs) are now being considered as a potential source of novel antimicrobial agents, which offer several advantages such as broad-spectrum activity and lower tendency to induce resistance (Rai et al. 2009).

Owing to their unique chemical and physical properties (Table 1) and high surface area-to-volume ratio, AgNPs possess many important biological activities (Duran and Marcato 2013; Rai and Ingle 2012) in particular, nano-silver has found its application in the treatment of wounds (Rigo et al. 2013), burns (Elliott 2010), in water-disinfecting systems (Zhang et al. 2012), in development of nano-containing materials for bone implants (Marsich et al. 2013), dental materials (Zhang et al. 2013) and as antibacterials (Dar et al. 2013), antivirals (Fayaz et al. 2012), anti-protozoals (Adhikari et al. 2013), anti-arthropods (Subarani et al. 2013) and anticancerous agents (Jeyaraj et al. 2013a, b). One of the main problems in anticancer treatments is the continuous growth of tumour cells resistant to a broad range of anticancer agents (Abraham et al. 2012). The documented activity of AgNPs against different

types of cancer cell lines, including multi-drug resistant cells, makes them a promising alternative to known anticancer agents (Conde et al. 2012).

Although the antibacterial properties of AgNPs are relatively well-known and have been exploited in many practical applications, their activities against other type of pathogens such as arthropod vectors of infections and different types of cancer cells have been evaluated only in recent years and there are still many open questions which require attention and further research.

The aim of the present review is to discuss the broad-spectrum bioactivities of AgNPs including their effects on different types of pathogenic micro- and macroorganisms, such as bacteria, viruses, fungi, protozoans and arthropods, as well as on tumour cells, to provide possible explanation of their mechanism of action, and to develop strategy for future studies in this area.

Antibacterial activity of silver nanoparticles

Antimicrobial properties of nano-silver have been known for many centuries but their evaluation on scientific basis has only started in 2000s years. Sondi and Salopek-Sondi (2004) were

Table 1 Shape and size of biologically (from some fungi and plants) and chemically synthesized silver nanoparticles

S.N.	Name of fungi and plants	Size (nm)	Shape	Reference
Fungi				
1	*Fusarium culmorum*	5–25	Spherical	Bawaskar et al. (2010)
2	*Phoma glomerata*	60–80	Spherical	Birla et al. (2009)
3	*Cryphonectria* sp.	30–70	Spherical	Dar et al. (2013)
4	*Fusarium oxysporum*	40.3±3.5	Spherical	De-Lima et al. (2013)
5	53 isolates of different fungi	5–50	Spherical	Devi and Joshi (2012)
6	*Opuntia ficus-indica*	12	Spherical	Gade et al. (2010)
7	*Alternaria alternata*	20–60	Spherical	Gajbhiye et al. (2009)
8	*Fusarium solani*	5–35	Spherical	Ingle et al. (2009)
9	*Aspergillus niger*	3–30	Spherical	Jaidev and Narasimha (2010)
10	*Pestalotia* sp.	10–40	Spherical	Raheman et al. (2011)
11	*Cochliobolus lunatus*	3–21	Spherical	Salunkhe et al. (2011)
Plants				
1	*Phytolacca decandra*	91	Spherical	Bhattacharyya et al. (2012)
2	*Murraya koenigii*	40–80	Spherical	Bonde et al. (2012)
3	*Sesbania grandiflora*	22	Spherical	Jeyaraj et al. (2013a)
4	*Podophyllum hexandrum*	14	Spherical	Jeyaraj et al. (2013b)
5	*Ocimum canum*	60–150	Rod	Jayaseelan and Rahuman (2012)
6	*Catharanthus roseus*	35–55	Spherical	Ponarulselvam et al. (2012)
7	*Vitex negundo*	30	Spherical	Prabhu et al. (2013)
8	*Vinca rosea*	25–47	Spherical	Subarani et al. (2013)
Chemical approaches				
1	Using plasma gas	10-80	Spherical	Roger et al. (2008)
2	Using PEG	11.23	Spherical	Shameli et al. (2012)

among the first to describe AgNPs activity against *Escherichia coli* and to propose a likely explanation of observed effects. The authors revealed formation of "pits" in bacterial cell wall and accumulation of AgNPs in the cellular membrane which led to an increase of its permeability and eventually to the death of bacterial cells. Also, they attempted to understand their mechanism of action. Presently, there are three main explanations that have been proposed to describe the antibacterial activity: (1) direct interaction of AgNPs with the bacterial cell membrane, causing subsequent membrane damage and complexation with components located inside the cells (Sondi and Salopek-Sondi 2004); (2) interaction with thiol (−SH) groups and production of reactive oxygen species (ROS) (Banerjee et al. 2010); (3) release of silver ions which inhibit respiratory enzymes and also generate ROS (Pal et al. 2007).

Devi and Joshi (2012) screened 53 strains of different fungi for the mycosynthesis of AgNPs and also reported significant efficacy against *S. aureus*, *Streptococcus pyogenes*, *Salmonella enterica* and *Enterococcus faecalis*. Moreover, the mycosynthesized nanoparticles also showed potent antibacterial activity and synergistic effect with erythromycin, methicillin, chloramphenicol and ciprofloxacin against *Klebsiella pneumoniae* and *Enterobacter aerogenes* (Bawaskar et al. 2010) and with antibiotics gentamycin, ampicillin, tetracycline and streptomycin against *E. coli*, *S. aureus* and *Pseudomonas aeruginosa* (Bonde et al. 2012).

Size-dependent activity of AgNPs was reported in many articles with smaller NPs having higher activity; this result may be explained by a relative increase in contact surface area (Liu et al. 2010). Shameli et al. (2012) demonstrated the antibacterial activity of different sizes of AgNPs in PEG against Gram-positive (*S. aureus*) and Gram-negative (*Salmonella typhimurium*) bacteria by the disc diffusion method. They reported the significant inhibition in growth of both these pathogens and concluded that the antibacterial activities of silver nanoparticles in PEG can be modified by controlling the size of nanoparticles because the activity of AgNPs decreases with the increase in the particle size.

All these factors that influence activity of AgNPs (concentration, size, shape, UV radiation and combination with different antibiotics) should be taken into account during synthesis processes and clinical use of AgNPs. Similarly, some other studies carried out by Birla et al. (2009), Gade et al. (2010), Ingle et al. (2008, 2009), Raheman et al. (2011), etc., had already proved the antibacterial potential of silver nanoparticles.

Antifungal activity of silver nanoparticles

Antifungal activity of AgNPs is less studied compared to antibacterial activity. This is clearly illustrated by the number of publications: the PubMed search on studies devoted to antibacterial activity of AgNPs revealed 590 published articles (up to May 2013), while number of antifungal studies was only 70, some of which are discussed below. Kim et al. (2008) studied the activity of chemically synthesized AgNPs against 44 strains of six fungal species viz. *Candida albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. krusei* and *Trichophyton mentagrophytes*. AgNPs showed potent activity against different strains of *T. mentagrophytes* and *Candida* sp.

Gajbhiye et al. (2009) reported effectiveness of biosynthesized silver nanoparticles against *Phoma glomerata*, *P. herbarum*, *Fusarium semitectum*, *Trichoderma* sp. and *C. albicans*. Further, they also reported the synergistic effects in combination with fluconazole. Jo et al. (2009) studied the activity of both silver ions and nanoparticles against two plant-pathogenic fungi, *Bipolaris sorokiniana* and *Magnaporthe grisea*. Antifungal activity of AgNPs in combination with different heterocyclic compounds like thiazolidine, phthalazine, pyrazolo, tetrazolo, hydrazide and pyridazine derivatives were studied against *Aspergillus flavus* and *C. albicans*. The results confirmed enhanced activity of AgNPs in combination with heterocyclic compounds as compared to heterocyclic compounds alone (Kandile et al. 2010). Similarly, Jaidev and Narasimha (2010) reported comparative activity of AgNPs against *Staphylococcus* sp., *Bacillus* sp., *E. coli* and *Aspergillus niger*. They reported higher zone of inhibition (1.2 cm) in case of *A. niger* confirming the maximum activity as compared to *Staphylococcus* sp. (0.9 cm), *Bacillus* sp. (0.8 cm) and *E. coli* (0.8 cm).

Nasrollahi et al. (2011) investigated antifungal activity of chemically synthesized AgNPs against *C. albicans* and *Saccharomyces cerevisiae*. Their results confirmed the potential activity of AgNPs as compared to standard antifungal agents (viz. amphotericin B and fluconazole). The changes on membrane reactions of yeasts have been elucidated by scanning electron microscopy. Savithramma et al. (2011) synthesized silver nanoparticles using extract of *Boswellia ovalifoliolata*, *Shorea tumbuggaia* and *Svensonia hyderobadensis*) and evaluated their antifungal activity against *A. flavus*, *A. niger*, *Curvularia* sp., *Fusarium* sp. and *Rhizopus* sp. The results showed that all the three nanoparticles synthesized from different medicinal plants have significant activity against all the tested fungi. Among these, nanoparticles synthesized from *Svensonia hyderobadensis* showed higher activity as compared to AgNPs synthesized using two other plants.

Kaur et al. (2012) studied potential antifungal activity of silver and chitosan nanoparticles against *Rhizoctonia solani*, *A. flavus*, and *Alternaria alternata* from chickpea seeds. In another study, Tile and Bholay (2012) reported significant activity of AgNPs against *C. albicans*, *Trichophyton rubrum* and *Aspergillus fumigatus*.

In an extensive study, Xu et al. (2013) evaluated AgNPs and natamycin against 216 strains of fungi from patients suffering from severe keratitis. These included 112 isolates of *Fusarium*, 82 isolates of *Aspergillus* and 10 *Alternaria* isolates. The authors reported that AgNPs demonstrated higher activity compared to natamycin. Recently, Dar et al. (2013) reported the remarkable antimicrobial activity of AgNPs synthesized from *Cryphonectria* sp. against *S. aureus*, *E. coli*, *Salmonella typhi* and *C. albicans*, concluding that AgNPs can be used as potential antifungal agents. In spite of various reports on antifungal activity of AgNPs, a precise mechanism of such effect has not been reported. One of possible explanations is destruction of membrane integrity of fungi and inhibition of normal budding process in yeasts (Kim et al. 2009). Similarly, in bacteria, disturbances in membrane penetration may also lead to internalization of nanoparticles and subsequent intracellular effects including ROS generation, interaction with -SH groups, inhibition of protein synthesis and interaction with phosphorus-containing molecules, such as DNA.

Antiviral activity of silver nanoparticles

AgNPs have received tremendous attention for their antibacterial activities, but the antiviral properties of metal nanoparticles remain an undeveloped area (Galdiero et al. 2013). Nowadays, effective and safe antiviral therapies are available and this has led to a significant improvement of the life for a large numbers of patients; nevertheless, viruses still represent one of the leading causes of the disease and death worldwide. Moreover, emerging and re-emerging viral diseases are a major threat to human and veterinary health. We have witnessed examples occurring approximately one each year, with the majority are viruses originating from an animal reservoir as a consequence of their ability to switch to a new host. The best known examples are SARS corona virus, West Nile virus, monkey pox virus, Hantavirus, Nipah virus, Hendravirus, Chikungunya virus and, last but not least, the threat of pandemic influenza viruses, most recently of avian or swine origin. Of the many factors responsible, changes to the local ecosystems that disturb the balance between pathogen and principal host species is one of the major drivers, together with increasing urbanization and changes in human behaviour (Howard and Fletcher 2012).

Therefore, there is a greater need to develop new and unique treatment options with antiviral agents, which can also overcome the problem of antiviral resistance. AgNPs are emerging as one of the options for the management of viral diseases due to their potential antiviral activity (Galdiero et al. 2011), and an important application of AgNPs is the treatment of viral diseases that require maintenance of circulating drug concentration or long lasting therapeutic regimens. AgNPs are active on a broad range of viruses and present a lower possibility of developing resistance compared to conventional antivirals.

The ideal antiviral agent should display a broad-spectrum action against many viral species/strains to be used as first aid compounds against unforeseen viral epidemics or pandemics and is greatly needed in the antiviral agents arsenal. Therefore, AgNPs have received considerable attention due to their particular intrinsic properties, especially since they have shown antiviral efficacy against several viruses regardless of the specific family. Nevertheless, different nanoparticles have different properties as a consequence of its production method (size, shape, capping agent and level of dispersity) and the available data from literature are quite heterogeneous and of difficult categorization. Three key aspects can be extrapolated from the studies conducted so far on the antiviral properties of AgNPs: (1) AgNPs have demonstrated antiviral activity against a number of viruses infecting both prokaryotic (De-Gusseme et al. 2010; Narasimha 2012) and eukaryotic organisms, making them a true broad-spectrum antiviral agent; (2) viral inhibition depends on the size of AgNPs (generally small AgNPs, 25 nm or less, resulted more active in viral infectivity inhibition) (Lara et al. 2010a; Speshock et al. 2010); (3) early infection might be the general time frame where AgNPs exert their antiviral activity impacting the rest of the viral replication cycle (Baram-Pinto et al. 2009; Trefry and Wooley 2013).

However, a precise mechanism of AgNP antiviral activity and an exact stage of infection at which AgNPs exert antiviral activity have yet to be determined. The possible general mechanism (Fig. 1) for the antiviral activity of silver nanoparticles can be derived by the available literature (see references throughout the section). Several studies have analysed the behaviour of naked (without a capping agent) AgNPs in inhibition of different viruses, namely hepatitis B virus (HBV) (Lu et al. 2008), influenza virus (Mehrbod et al. 2009; Xiang et al. 2011), human parainfluenza virus type 3 (HPIV-3) (Gaikwad et al. 2013), Herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2) (Gaikwad et al. 2013; Sun et al. 2005), Coxsackievirus B3 (Salem et al. 2012), tacaribe virus (TCRV) (Speshock et al. 2010), Vaccinia virus (Trefry and Wooley 2013) and monkeypox virus (MPV) (Roger et al. 2008). A general plot of the activity of naked nanoparticles against these viruses is difficult to draw as a consequence of different AgNPs production procedures and their different sizes. In fact, though being able to inhibit Coxakievirus B3 infectivity with a dose–response effect (Salem et al. 2012), the nanoparticles derived from *Ricinus communis* aqueous extracts measured up to 1,000 nm, therefore, could be barely considered nanoparticles. Other AgNPs produced by fungi were more contained in size (size range 5–20 nm) and showed a consistent ability to reduce infectivity of HSV-1/2 and HPIV-3 (Gaikwad et al. 2013). Production of antiviral AgNPs
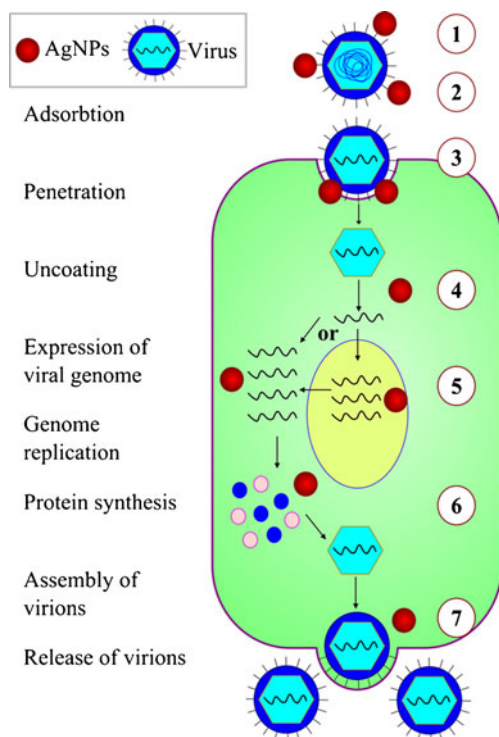
Fig. 1 Mechanism of antiviral effect of AgNPs on different stages of virus replication: *1*—interaction with viral surface, *2*—interference with viral attachment, *3*—inhibition of virus penetration into the cell, *4*—interaction with viral genome, *5*—inhibition of genome replication, *6*—inhibition of protein synthesis, *7*—inhibition of assembly and release of virions

from different fungi is a feasible method, but some of the fungi strains resulted in production of silver nanoparticles with considerable toxicity. Nanoparticles produced in *Fusarium oxysporum*, *Curvularia* sp. and *Chaetomium indicum* presented low toxicity levels and promising antiviral activity.

Lu et al. (2008) demonstrated that larger nanoparticles (800 nm) presented high level of cytotoxicity in cell culture-based assays, but smaller nanoparticles only showed minor toxicity, in fact, HBV could be efficiently inhibited by 10 and 50 nm nanoparticles where the activity was probably due to specific interactions between the nanoparticles and the double-stranded DNA of HBV and/or direct binding with viral particles and consequent prevention of virions from entering into host cells. In this study, antiviral testing and cytotoxicity assays were performed using HepAD38, a stably transfected hepatoblastoma cell line that secretes HBV-like particles and express high levels of HBV DNA into the supernatant. Similarly, influenza virus can be efficiently inhibited by AgNPs of average size of 10 nm (Xiang et al. 2011). Naked AgNPs could provide a strong protection against influenza virus infections without the risk of cell toxicity (Mehrbod et al. 2009; Xiang et al. 2011). Another study is focused on TCRV of the Arenaviridae family and has shown an excellent activity of 10 nm particles compared to 25 nm particles (Speshock et al.

2010). AgNPs seem to interact with TCRV prior to cellular exposure resulting in either prevention of the viral particle internalization by interfering with cellular receptor binding or may favour the internalization of the AgNP together with the virus and produce an inhibitory effect on viral replication interfering with the TCRV RNA-dependent RNA polymerase.

The overall picture shows a tendency of the smaller size nanoparticles to be more incisive in reducing infectivity regardless of the viral species and to exert a minor cytotoxicity. Capping agent(s) added to naked silver nanoparticles (polyvinylpyrrolidone, citrate and polyethylene glycol, etc.) have also been proven to be biologically compatible and reduce infectivity; however, they may render the AgNPs less efficacious. In fact, a polysaccharide coating protects the cell from the toxic effects of the AgNPs, but it also reduces its activity against TCRV (Speshock et al. 2010). Indeed, the same capping agent proved to be very efficacious against MPV, where polysaccharide-coated AgNPs of 10 nm were highly effective in reducing MPV-induced plaque formation in vitro at concentrations ranging from 12.5 to 100 μg/mL (Roger et al. 2008).

Other examples of coated AgNPs are offered in several studies having as antiviral target human immunodeficiency virus type-1 (HIV-1) (Lara et al. 2010a, b, 2011; Sun et al. 2005), HSV (Baram-Pinto et al. 2009) and respiratory syncytial virus (RSV) (Sun et al. 2008). AgNPs with a surface coating of poly(N-vinyl-2-pyrrolidone) (PVP) within the range of 1–10 nm proved to be the most efficacious nanoparticles to inhibit replication of HIV in a dose-dependent manner (Elechiguerra et al. 2005). AgNPs were able to inhibit a number of HIV-1 isolates (including laboratory strains, clinical isolates, macrophage [M]-tropic and T lymphocyte [T]-tropic strains, and resistant strains) suggesting they may be broad-spectrum anti-HIV-1 agents (Lara et al. 2010a). In fact, PVP-coated silver nanoparticles have been tested as a topical vaginal microbicide endowed with virucidal activity to prevent transmission of HIV-1 infection using an in vitro human cervical tissue-based organ culture that simulates in vivo conditions (Lara et al. 2010b) or as coating for polyurethane condoms to directly inactivate infectious microorganisms (Fayaz et al. 2012). Both studies proved to sensibly inactivate HIV infectivity. The precise mechanism of action is not completely understood, but several data point to a direct interaction of AgNPs with surface glycoproteins and interference with binding and fusion events of viral penetration into susceptible cells. Furthermore, AgNPs are able to inhibit post-entry stages of the HIV-1 life cycle; in fact, the antiviral activity can also be maintained when the silver nanoparticles were added after the cell had been already infected with HIV. In this event, AgNPs might inhibit post-entry stages of infection by blocking other functional HIV-1 proteins or reducing reverse transcription or proviral transcription rates by directly binding to the RNA or DNA molecules. Also, RSV can be

efficiently inhibited by PVP-coated AgNPs (Sun et al. 2008), probably by binding of nanoparticles to the viral surface through a possible interaction with entry glycoproteins that are evenly distributed on the envelope of the RSV virion. A different capping agent, namely mercaptoethanesulfonate (Baram-Pinto et al. 2009), has been used as capping agent for AgNPs tested against HSV-1. Sulfonate-capped AgNPs inhibit HSV-1 infection by blocking the attachment and thereby the entrance of the virus into the cells and/or by preventing the cell-to-cell spread of the virus. Their anti-HSV-1 activity depends from their ability to mimic heparan sulphate (the cellular primary receptor for HSV) and thus compete for the binding of the virus to the cell and is amplified by the presence of the inner core of nanosilver.

The exploitation of AgNPs as antivirals is still in its infancy, and further studies are warranted to elucidate the mechanism(s) of action, which may render possible antiviral development of AgNPs to fill the vital niche of a broad-spectrum antiviral agent.

Anti-protozoal activity of silver nanoparticles

Oocyst-producing water-borne intestinal protozoa, such as *Giardia lamblia* and especially *Cryptosporidium parvum*, are resistant to traditional deactivation procedures including size-exclusion filters and chlorine treatments (Korich et al. 1990). Both the pathogens cause gastrointestinal infections throughout the world. Furthermore, infection of *Cryptosporidium parvum* in immune-compromised individuals can be life-threatening; thus, search for new methods of deactivation of these pathogens at ultra-low detection level has great importance.

An interesting in vivo study was carried out by Said et al. (2012) who compared the activity of AgNPs, chitosan NPs and curcumin NPs against *G. lamblia* in experiments on rats. The maximum efficacy was achieved by combining all three types of nanoparticles (AgNPs, chitosan NPs and curcumin NPs) compared to when they were used separately. Experiments are being performed to verify the effectiveness of AgNPs against *Cryptosporidium parvum* (Abebe 2012; Su et al. 2012). The study by Abebe (2012) is directed to assess disinfection effect of AgNPs on *Cryptosporidium parvum* and to develop an effective system of water filtration. However, final results of both experimental studies have not yet been published.

Another important protozoal infection is leishmaniasis, which is one of the main neglected tropical infections of the world with occurrence in 88 countries and an estimated number of 500,000 cases of visceral form and 1.5 million cases of cutaneous leishmaniasis (Marr et al. 2012). Drug resistance compromises present treatment options and absence of effective vaccination warrants to search for new compounds with

anti-leishmanial activity. Nanotechnology is implied in two different directions: the development of nano-liposomal formulations containing conventional anti-leishmanial drugs, for instance, antimonial and amphotericin B liposomes (Duran et al. 2009), and the use of nanoparticles of metals or metal oxides, including AgNPs, Ag_2O and TiO_2 nanoparticles (Allahverdiyev et al. 2011a, b, c).

Leishmania parasites are sensitive to ROS (Murray 1981); however, during multiplication in macrophages they block enzymatic mechanisms responsible for ROS production and thus evade destruction (Shio and Olivier 2010). One of the first works on anti-leishmanial activity of AgNPs did not find significant differences in reducing proliferation of *Leishmania major* by AgNPs and controls in in vitro experiments, and also there was no significant decrease in lesion sizes and amastigote counts in the in vivo experiment on BALB/c mice; however, nanosilver-treated mice demonstrated significant decrease in secondary infection. Therefore, it was concluded that AgNPs are effective to control the secondary infection in localized cutaneous leishmaniasis (Mohebali et al. 2009). Similar results regarding lesion sizes and splenic parasite load were obtained by Nilforoushzadeh et al. (2012); there were no significant differences in these parameters in groups treated using chemically produced AgNPs compared with the control group without treatment.

However, Rossi-Bergmann et al. (2012) reported promising activity of biosynthesized (using *F. oxysporum*) AgNPs against *Leishmania amazonensis* promastigotes in vitro and in vivo. Further, they also compared activity of biologically and chemically produced AgNPs. It was observed that in in vitro experiments biologically produced AgNPs were four times more potent than chemically produced AgNPs; moreover, in the in vivo model they were even more effective.

In another recent study, in vitro effect of AgNPs on morphological properties, growth, proliferation, metabolic activity, infectivity and infection index (percentage of infected macrophages multiplied by the average number of amastigotes per macrophage) of *Leishmania tropica* was evaluated depending on presence or absence of UV irradiation (Allahverdiyev et al. 2011b). AgNPs inhibited all biological activities of *L. tropica* and, moreover, this effect was enhanced under UV light. Observed enhancing effect of UV light on anti-leishmanial activity of AgNPs was attributed to the ability of AgNPs to release silver ions. Loosing infectious ability by *Leishmania* under the action of AgNPs, especially noted together with UV light, was explained by interaction of AgNPs with parasitic surface lipophosphoglycan and glycoprotein molecules that are responsible for infectivity. Such findings are important not only in the treatment of leishmaniasis but also in the control of its spread by application of AgNPs on sandfly vectors carrying infective promastigotes. Interestingly, amastigotes appeared to be more sensitive than promastigotes, even to low concentrations of AgNPs that are non-harmful for

macrophages, such as 1–10 mg/L. This was supposed to be a result of macrophages action, which after exposure to AgNPs may enhance production of lytic enzymes or nitric oxide, and also this effect may be caused by losing ability of amastigotes to affect negatively the ROS production.

One of the most common protozoal vector-borne diseases with prevalence in tropical and subtropical regions and over one million global deaths per year is malaria (Kamareddine 2012). Rapid growth in resistance of plasmodia to antimalarial drugs stimulates continuous search for innovative approaches against malarial parasites, and also for methods to control the spread of the mosquito vector.

Among different agents, AgNPs have also been evaluated against plasmodia in several works that demonstrated promising results. Panneerselvam et al. (2011) reported activity of AgNPs (average size of approximately 55 nm) produced biologically using *Andrographis paniculata* Nees (Acanthaceae) against *P. falciparum*. Ponarulselvam et al. (2012) reported activity of AgNPs (average size of approximately 35–55 nm) produced using aqueous leaves extract of *Catharanthus roseus* against *P. falciparum*. An ongoing study of Murugan et al. (2013) demonstrates high activity of AgNPs bio-reduced in 5 % *Cassia occidentalis* leaf broth against chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* and malaria vector *Anopheles stephensi*. However, there is no explanation of anti-plasmodial effects in any published studies.

Anti-arthropod activity of AgNPs

In recent years, there has been increasing incidence of many vector-borne pathogens in new geographical regions (Kilpatrick and Randolph 2012). Resistance to insecticidal agents was found among all types of arthropod vectors. Ticks were found to be resistant to acaricides; moreover, present acaricidal substances have serious drawbacks, such as contamination of environment, milk and meat products (Jayaseelan and Rahuman 2012). The same happens with insecticide resistance in mosquitoes and lice (Raghavendra et al. 2011; Durand et al. 2012). Owing to this, interest of scientists has been devoted to the search for anti-arthropod potential in different types of antiparasitic agents, including AgNPs (Adhikari et al. 2013). Many recently published studies report significant acaricidal, larvicidal and lousicidal properties in biologically produced AgNPs, proving that they represent an innovative approach to control arthropods and prevent spread of vector-borne diseases.

In spite of the fact that many published studies proved anti-arthropodal effect of AgNPs, there is still no clear scientific explanation of it. The possible larvicidal activity of AgNPs was hypothesized to be caused by penetration of nanoparticles through larvae membrane (Salunkhe et al. 2011); however,

further studies are necessary in order to reveal the precise mechanism of anti-arthropod activity of AgNPs.

Silver nanoparticles in cancer

The early detection and treatment of cancer are the basic problems faced by the cancer specialists and hence this area has attracted a great attention. One important point in the effectiveness of anti-cancer drugs is related to the possibility of reaching the target site in sufficient concentration and to the efficient activity without causing damage to healthy tissues and cells (Misra et al. 2010; Seigneuric et al. 2010).

In this direction, nanotechnology represents, at the moment, one of the new technologies with possibility to enhance the diagnosis and treatment of cancer. This could be achieved through new imaging agents, multifunctional targeted devices capable of bypassing biological barriers to deliver therapeutic agents directly to the biological target involved in cancer, nano-biosensors for predicting the disease and minimizing the growth of cancer cells and reducing the cost of treatments (Jain 2010; Qiao et al. 2010). Metallic nanoparticles, in this area, appear as important agents, since they are used in several biomedical applications, such as highly sensitive diagnostic assays and biosensors (Rai et al. 2012), thermal, and radiotherapy enhancement (Qiao et al. 2010), as well as drug and gene delivery with relatively low toxicity (Bhattacharyya et al. 2012; Conde et al. 2012). It is known that AgNPs interact with cells and intracellular macromolecules like proteins and DNA, probably through ROS, showing apoptotic bodies and necrotic cell death due to the cytotoxicity of biogenic AgNPs,
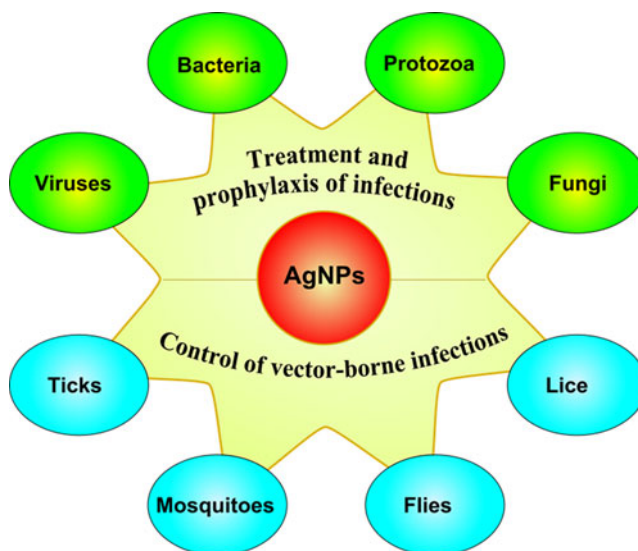

Fig. 2 AgNPs in the treatment and control of infectious diseases: antimicrobial properties of AgNPs make them useful in the treatment and prophylaxis of infections (*upper part* of diagram), while anti-arthropod properties can be used in the control of spread of infections by affecting arthropod vectors (down part of diagram)

although all of these possibilities are still under studies (Duran et al. 2010; Jeyaraj et al. 2013a, b). Several factors influence toxicity of AgNPs, such as dose, time and size of the particles. Against MCF-7 cell culture, it was found that toxicity is dose-dependent and causes cellular damage in Human Epidermoid Larynx (Hep-2) cell line through ROS formation (Jacob et al. 2012). Biologically synthesized AgNPs from the leaf of *Suaeda monoica* on Hep-2 cells exhibited dose-dependent toxicity at the concentration studied (Satyavani et al. 2012).

AgNPs biogenically synthesized from *Podophyllum hexandrum* leaf extract showed a cytotoxicity and apoptotic effect, probably through caspace-cascade activation and loses of mitochondrial integrity (Jeyaraj et al. 2013b). Piao et al. (2011) reported that hydroxyl radicals released by the AgNPs attack cellular components including DNA, lipids and proteins to cause various kinds of oxidative damages. Jeyaraj et al. (2013a) using biogenic AgNPs from *Sesbania grandiflora* leaf extract also showed cytotoxic effect against MCF-7 cell lines inducing cellular damage in terms of loss of cell membrane integrity, oxidative stress and apoptosis. The authors suggested that in order to progress to clinical cancer treatment it is necessary to study the formulation and clinical trials to establish the nanodrug to treat cancer cells.

In a recent study, biogenic AgNPs from *Vitex negundo* leaf extract showed inhibition of proliferation of human colon cancer cell line HCT15. These results indicate that AgNPs may exert antiproliferative effects on colon cancer cell line by suppressing its growth, arresting the G0/G1-phase, reducing DNA synthesis and inducing apoptosis (Prabhu et al. 2013). Inoculation of Dalton's lymphoma ascites cells in mice produced a tumour progression in the animals, whereas in the presence of AgNPs a substantial decrease in cancer cell numbers in tumour mice was observed through histopathologic analysis. Apparently, the effect of AgNPs in increasing mean survival time and life span depends on their ability to reduce tumour cell viability and induce cytotoxicity (Sriram et al. 2010). The hematologic parameters examined in the controls, tumour controls and tumour-treated mice showed the effect of AgNPs in reducing white blood cell and platelet counts in tumour-bearing mice compared with controls. These data highlight the non-toxic effect of AgNPs, which did not induce any alteration in hematologic parameters for treated mice in comparison with controls and, at the same time, led to effective control of white blood cells that possess the immunologic constituents of ascitic fluid. This was corroborated recently by De-Lima et al. (2012, 2013) in cytotoxic and genotoxic biogenic AgNPs studies.

Conclusions and future prospects

AgNPs demonstrated broad-spectrum activity against different types of causative agents of infectious diseases, and also against their arthropod vectors, which makes it possible to apply AgNPs not only for treatment purposes but also for control of infections (Fig. 2). Recent studies have been directed to address several questions: (1) methods of synthesis of AgNPs with optimal properties enhancing their antimicrobial effect and minimizing potential adverse toxic impact on human or animal cells; (2) detection of possible targets among microorganisms, against which AgNPs can be potentially applied either alone or in combination with conventional antimicrobial agents; (3) detection of possible candidates among arthropod vectors transmitting infections taking into account the stages of their life cycle which can be easily and effectively targeted; (4) producing clinically and environmentally applicable forms containing AgNPs, such as antimicrobial coatings against microorganisms or repellent substances against their arthropod vectors. Many aspects in these global goals still remain unsolved and studies in the nearest future may help in overcoming present to-date barriers. Studies on combined use of AgNPs with other antimicrobial agents may solve problem of toxicity and prevent possible risk of resistance development. Further investigations should also be devoted to the assessment of influence of biological fluids, oxygen pressure and other chemical and biological factors on bioactivity and biocompatibility of AgNPs. Mechanism of antimicrobial and anti-arthropod effect should be deeply evaluated, as understanding of all molecular events in action of AgNPs may open up new perspectives in their application and new possibilities of creating beneficial combinations with other biologically active agents.

Broad-spectrum bioactivities of AgNPs make them promising agents not only in fighting infections but also in tackling serious problem of tumours and, particularly, multi-drug-resistant cancer cells. AgNPs can be used in the diagnostics and treatment of different cancers. Many anti-cancer research are in progress in in vitro assay and a few on in vivo studies. Therefore, this is an open area for many new studies in the cancer treatment with AgNPs.

References

Abebe L (2012) Silver impregnated ceramic water filters to treat *Cryptosporidium parvum*. CGH Symposium, 1 October 2012. http://prezi.com/fx_3-9w4ai0h/silver-nanoparticle-treated-cryptosporidium-parvum-response-in-mice/. Accessed 26 March 2013

Abraham I, El-Sayed K, Chen ZS, Guo H (2012) Current status on marine products with reversal effect on cancer multidrug resistance. Mar Drugs 10:2312–2321

Adhikari U, Ghosh A, Chandra G (2013) Nanoparticles of herbal origin: a recent eco-friend trend in mosquito control. Asian Pac J Trop Dis 3: 167–168

Allahverdiyev AM, Abamor ES, Bagirova M, Rafailovich M (2011a) Antimicrobial effects of TiO_2 and Ag_2O nanoparticles against

drug-resistant bacteria and leishmania parasites. Future Microbiol 6: 933–940

Allahverdiyev AM, Abamor ES, Bagirova M, Ustundag CB, Kaya C, Kaya F, Rafailovich M (2011b) Antileishmanial effect of silver nanoparticles and their enhanced antiparasitic activity under ultraviolet light. Int J Nanomedicine 6:2705–2714

Allahverdiyev AM, Kon KV, Abamor ES, Bagirova M, Rafailovich M (2011c) Coping with antibiotic resistance: combination of nanoparticles with antibiotics and other antimicrobial agents. Expert Rev Anti-Infect Ther 9:1035–1052

Banerjee M, Mallick S, Paul A, Chattopadhyay A, Ghosh SS (2010) Heightened reactive oxygen species generation in the antimicrobial activity of a three component iodinated chitosan-silver nanoparticle composite. Langmuir 26:5901–5908

Baram-Pinto D, Shukla S, Perkas N, Gedanken A, Sarid R (2009) Inhibition of herpes simplex virus type 1 infection by silver nanoparticles capped with mercaptoethane sulfonate. Bioconjug Chem 20:1497–1502

Bawaskar M, Gaikwad S, Ingle A, Rathod D, Gade A, Duran N, Marcato PD, Rai M (2010) A new report on mycosynthesis of silver nanoparticles by *Fusarium culmorum*. Curr Nanosci 6:376–380

Bhattacharyya SS, Das J, Das S, Samadder A, Das D, De A, Paul S, Khuda-Bukhsh AR (2012) Rapid green synthesis of silver nanoparticles from silver nitrate by a homeopathic mother tincture phytolacca decandra. Zhong Xi Yi Jie He Xue Bao 10:546–554

Birla SS, Tiwari VV, Gade AK, Ingle AP, Yadav AP, Rai MK (2009) Fabrication of silver nanoparticles by *Phoma glomerata* and its combined effect against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Lett Appl Microbiol 48:173–179

Bonde SR, Rathod DP, Ingle AP, Ade RB, Gade AK, Rai MK (2012) *Murraya koenigii*-mediated synthesis of silver nanoparticles and its activity against three human pathogenic bacteria. Nanosci Meth 1: 25–36

Conde J, Doria G, Baptista P (2012) Noble metal nanoparticles applications in cancer. J Drug Deliv 751075:1–12

Dar MA, Ingle A, Rai M (2013) Enhanced antimicrobial activity of silver nanoparticles synthesized by *Cryphonectria* sp. evaluated singly and in combination with antibiotics. Nanomedicine NBM 9:105–110

De-Gusseme B, Sintubin L, Baert L, Thibo E, Hennebel T, Vermeulen G, Uyttendaele M, Verstraete W, Boon N (2010) Biogenic silver for disinfection of water contaminated with viruses. Appl Environ Microbiol 76:1082–1087

De-Lima R, Seabra AB, Durán N (2012) Silver nanoparticles: a brief review of cytotoxicity and genotoxicity of chemically and biogenically synthesized nanoparticles. J Appl Toxicol 32:867–879

De-Lima R, Feitosa LO, Ballottin D, Marcato PD, Tasic L, Durán N (2013) Cytotoxicity and genotoxicity of biogenic silver nanoparticles. J Phys Conf Series 429:012020

Devi LS, Joshi SR (2012) Antimicrobial and synergistic effects of silver nanoparticles synthesized using soil fungi of high altitudes of Eastern Himalaya. Mycobiol 40:27–34

Duran N, Marcato PD (2013) Nanobiotechnology perspectives: role of nanotechnology in the food industry: a review. Int J Food Sci Technol 48:1127–1134

Duran N, Marcato PD, Teixeira Z, Durán M, Costa FTM, Brocchi M (2009) State of the art of nanobiotechnology applications in neglected diseases. Curr Nanosci 5:396–408

Duran N, Marcato PD, De-Conti R, Alves OL, Costa FTM, Brocchi M (2010) Potential use of silver nanoparticles on pathogenic bacteria, their toxicity and possible mechanisms of action. J Braz Chem Soc 21:949–959

Durand R, Bouvresse S, Berdjane Z, Izri A, Chosidow O, Clark JM (2012) Insecticide resistance in head lice: clinical, parasitological and genetic aspects. Clin Microbiol Infect 18:338–344

Elechiguerra JL, Burt JL, Morones JR, Camacho-Bragado A, Gao X, Lara HH, Yacaman MJ (2005) Interaction of silver nanoparticles with HIV-1. J Nanobiotechnol 3:6

Elliott C (2010) The effects of silver dressings on chronic and burns wound healing. Br J Nurs 19:S32–S36

Fall B, Pascual A, Sarr FD, Wurtz N, Richard V, Baret E, Diémé Y, Briolant S, Bercion R, Wade B, Tall A, Pradines B (2013) Plasmodium falciparum susceptibility to antimalarial drugs in Dakar, Senegal, in 2010: an ex vivo and drug resistance molecular markers study. Malar J 12:107

Fayaz AM, Ao Z, Girilal M, Chen L, Xiao X, Kalaichelvan P, Yao X (2012) Inactivation of microbial infectiousness by silver nanoparticles-coated condom: a new approach to inhibit HIV- and HSV-transmitted infection. Int J Nanomedicine 7:5007–5018

Gade A, Gaikwad S, Tiwari V, Yadav A, Ingle A, Rai M (2010) Biofabrication of silver nanoparticles by *Opuntia ficus-indica*: in vitro antibacterial activity and study of the mechanism involved in the synthesis. Curr Nanosci 6:370–375

Gaikwad S, Ingle A, Gade A, Rai M, Falanga A, Incoronato N, Russo L, Aldiero S, Galdiero M (2013) Antiviral activity of mycosynthesized silver nanoparticles against herpes simplex virus and human parainfluenza virus type 3. Int J Nanomedicine 3(8):4303–4314

Gajbhiye MB, Kesharwani JG, Ingle AP, Gade AK, Rai MK (2009) Fungus mediated synthesis of silver nanoparticles and its activity against pathogenic fungi in combination of fluconazole. Nanomedicine NBM 5:282–286

Galdiero S, Falanga A, Vitiello M, Marra MCV, Galdiero M (2011) Silver nanoparticles as potential antiviral agents molecules. Molecules 16: 8894–8918

Galdiero S, Falanga A, Cantisani M, Ingle A, Galdiero M, Rai M (2014) Silver nanoparticles as novel antibacterial and antiviral agents, In: Frontiers of Nanomedical Research, Worlds Scientific Publishing 2014, in press

Howard CR, Fletcher NF (2012) Emerging virus diseases: can we ever expect the unexpected? Emerg Microbes Infect 1:e46

Ingle A, Gade A, Pierrat S, Sonnichsen C, Rai M (2008) Mycosynthesis of silver nanoparticles using the fungus *Fusarium acuminatum* and its activity against some human pathogenic bacteria. Curr Nanosci 4: 141–144

Ingle A, Rai M, Gade G, Bawaskar M (2009) *Fusarium solani*: a novel biological agent for the extracellular synthesis of silver nanoparticles. J Nanopart Res 11:2079–2085

Jacob SJP, Finu JS, Narayanan A (2012) Synthesis of silver nanoparticles using *Piper longum* leaf extracts and its cytotoxic activity against Hep-2 cell line. Colloids Surf B: Biointerfaces 91:212–214

Jaidev LR, Narasimha G (2010) Fungal mediated biosynthesis of silver nanoparticles, characterization and antimicrobial activity. Colloids Surf B: Biointerfaces 81:430–433

Jain KK (2010) Advances in the field of nano-oncology. BMC Med 8:1–11

Jayaseelan C, Rahuman AA (2012) Acaricidal efficacy of synthesized silver nanoparticles using aqueous leaf extract of *Ocimum canum* against *Hyalomma anatolicum anatolicum* and *Hyalomma marginatum isaaci* (*Acari*: *Ixodidae*). Parasitol Res 111:1369–1378

Jayaseelan C, Rahuman AA, Rajakumar G, Santhoshkumar T, Kirthi AV, Marimuthu S, Bagavan A, Kamaraj C, Zahir AA, Elango G, Velayutham K, Rao KV, Karthik L, Raveendran S (2012) Efficacy of plant-mediated synthesized silver nanoparticles against hematophagous parasites. Parasitol Res 111:921–933

Jeyaraj M, Rajesh M, Arun R, MubarakAli D, Sathishkumar G, Sivanandhan G, Dev KG, Manickavasagam M, Premkumar K, Thajuddin N, Ganapathi A (2013a) An investigation on the cytotoxicity and caspase-mediated apoptotic effect of biologically synthesized silver nanoparticles using *Podophyllum hexandrum* on human cervical carcinoma cells. Colloids Surf B: Biointerfaces 102:708–717

Jeyaraj M, Sathishkumar G, Sivanandhan G, Mubarak-Ali D, Rajesh M, Arun R, Apildev G, Manickavasagam M, Thajuddin N, Premkumar K, Ganapathi A (2013b) Biogenic silver nanoparticles for cancer treatment: an experimental report. Colloids Surf B: Biointerfaces 106:86–92

Jo YK, Kim BH, Jung G (2009) Antifungal activity of silver ions and nanoparticles on phytopathogenic fungi. Plant Dis 93:1037–1043

Johnson AP (2011) Methicillin resistant *Staphylococcus aureus*: the European landscape. J Antimicrob Chemother 66:iv43–iv48

Johnson VA, Calvez V, Gunthard HF, Paredes R, Pillay D, Shafer RW, Wensing AM, Richman DD (2013) Update of the drug resistance mutations in HIV-1: March 2013. Top Antivir Med 21:6–14

Kamareddine L (2012) The biological control of the malaria vector. Toxins (Basel) 4:748–767

Kandile NG, Zaky HT, Mohamed MI, Mohamed HM (2010) Silver nanoparticles effect on antimicrobial and antifungal activity of new heterocycles. Bull Kor Chem Soc 31:3530–3538

Kaur P, Thakur R, Choudhary A (2012) An in vitro study of the antifungal activity of silver/chitosan nanoformulations against important seed borne pathogens. Int J Sci Technol Res 1:83–86

Kilpatrick AM, Randolph SE (2012) Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. Lancet 380:1946–1955

Kim KJ, Sung WS, Moon SK, Choi JS, Kim JG, Lee DG (2008) Antifungal effect of silver nanoparticles on dermatophytes. J Microbiol Biotechnol 18:1482–1484

Kim KJ, Sung WS, Suh BK, Moon SK, Choi JS, Kim JG, Lee DG (2009) Antifungal activity and mode of action of silver nano-particles on *Candida albicans*. Biometals 22:235–242

Korich DG, Mead JR, Madore MS, Sinclair NA, Sterling CR (1990) Effects of ozone, chlorine dioxide, chlorine, and monochloramine on *Cryptosporidium parvum* oocyst viability. Appl Environ Microbiol 56:1423–1428

Lara HH, Ayala-Nunez NV, Ixtepan-Turrent L, Rodriguez-Padilla C (2010a) Mode of antiviral action of silver nanoparticles against HIV-1. J Nanobiotechnol 8:1

Lara HH, Ixtepan-Turrent L, Garza-Treviño EN, Rodriguez-Padilla C (2010b) PVP-coated silver nanoparticles block the transmission of cell-free and cell-associated HIV-1 in human cervical culture. J Nanobiotechnol 8:15–25

Lara HH, Ixtepan-Turrent L, Garza-Treviño EN, Singh DK (2011) Use of silver nanoparticles increased inhibition of cell-associated HIV-1 infection by neutralizing antibodies developed against HIV-1 envelope proteins. J Nanobiotechnol 9:38

Liu HL, Dai SA, Fu KY, Hsu SH (2010) Antibacterial properties of silver nanoparticles in three different sizes and their nanocomposites with a new waterborne polyurethane. Int J Nanomedicine 5:1017–1028

Lu L, Sun RW, Chen R, Hui CK, Ho CM, Luk JM, Lau GK, Che CM (2008) Silver nanoparticles inhibit hepatitis B virus replication. Antivir Ther 13:253–262

Marr AK, McGwire BS, McMaster WR (2012) Modes of action of leishmanicidal antimicrobial peptides. Future Microbiol 7:1047–1059

Marsich E, Travan A, Donati I, Turco G, Kulkova J, Moritz N, Aro HT, Crosera M, Paoletti S (2013) Biological responses of silver-coated thermosets: an in vitro and in vivo study. Acta Biomater 9:5088–5099

Mehrbod P, Motamed N, Tabatabaian M, Soleimani ER, Amini E, Shahidi M, Kheiri MT (2009) In vitro antiviral effect of "nanosilver" on influenza virus. DARU 17:88–93

Misra R, Acharya S, Sahoo SK (2010) Cancer nanotechnology: application of nanotechnology in cancer therapy. Drug Discov Today 15:842–850

Mohebali M, Rezayat MM, Gilani K, Sarkar S, Akhoundi B, Esmaeili J, Satvat T, Elikaee S, Charehdar S, Hooshyar H (2009) Nanosilver in the treatment of localized cutaneous leishmaniasis caused by *Leishmania major* (MRHO/IR/75/ER): an in vitro and in vivo study. DARU J Pharm Sci 17:285–289

Murray HW (1981) Susceptibility of *Leishmania* to oxygen intermediates and killing by normal macrophages. J Exp Med 153:1302–1315

Murugan K, Shri KP, Barnard D (2013) Green synthesis of silver nanoparticles from botanical sources and their use for control of medical insects and malaria parasites. http://www.ars.usda.gov/research/publications/publications.htm?seq_no_115=281989. Accessed 26 March 2013

Narasimha G (2012) Antiviral activity of silver nanoparticles synthesized by fungal strain *Aspergillus niger*. J Nanosci Nanotechnol 6(1):18–20

Nasrollahi A, Pourshamsian K, Mansourkiaee P (2011) Antifungal activity of silver nanoparticles on some of fungi. Int J Nanotechnol 1:233–239

Nilforoushzadeh MA, Shirani-Bidabadi LA, Zolfaghari-Baghbaderani A, Jafari R, Heidari-Beni M, Siadat A, Ghahraman-Tabrizi M (2012) Topical effectiveness of different concentrations of nanosilver solution on *Leishmania major* lesions in balb/c mice. J Vector Borne Dis 49:249–253

Pal S, Tak UK, Song JM (2007) Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the gram-negative bacterium *Escherichia coli*. Appl Environ Microbiol 73:1712–1720

Panneerselvam C, Ponarulselvam S, Murugan K (2011) Potential anti-plasmodial activity of synthesized silver nanoparticle using *Andrographis paniculata* nees (Acanthaceae). Archives of Applied Science Research 3(6):208–217

Piao MJ, Kang KA, Lee IK, Kim HS, Kim S, Choi YJ, Choi J, Hyun JW (2011) Silver nanoparticles induce oxidative cell damage in human liver cells through inhibition of reduced glutathione and induction of mitochondria-involved apoptosis. Toxicol Lett 201:92–100

Ponarulselvam S, Panneerselvam C, Murugan K, Aarthi N, Kalimuthu K, Thangamani S (2012) Synthesis of silver nanoparticles using leaves of *Catharanthus roseus* Linn. G. Don and their antiplasmodial activities. Asian Pac J Trop Biomed 2:574–580

Prabhu D, Arulvasu C, Babu G, Manikandan R, Srinivasan P (2013) Biologically synthesized green silver nanoparticles from leaf extract of *Vitex negundo* L. induce growth-inhibitory effect on human colon cancer cell line HCT15. Process Biochem 48:317–324

Qiao W, Wang B, Wang Y, Yang L, Zhang Y, Shao P (2010) Cancer therapy based on nanomaterials and nanocarrier systems. J Nanomater 796303:1–9

Raghavendra K, Barik TK, Reddy BP, Sharma P, Dash AP (2011) Malaria vector control: from past to future. Parasitol Res 108:757–779

Raheman F, Deshmukh S, Ingle A, Gade A, Rai M (2011) Silver nanoparticles: novel antimicrobial agent synthesized from an endophytic fungus *Pestalotia* sp. isolated from leaves of *Syzygium cumini* (L). Nano Biomed Eng 3(3):174–178

Rai M, Ingle A (2012) Role of nanotechnology in agriculture with special reference to management of insect pests. Appl Microbiol Biotechnol 94:287–293

Rai MK, Yadav AP, Gade AK (2009) Silver nanoparticles as a new generation of antimicrobials. Biotechnol Adv 27:76–82

Rai M, Gade A, Gaikwad S, Marcato PD, Durán N (2012) Biomedical applications of nanobiosensors: the state-of-the-art. J Braz Chem Soc 23:14–24

Rigo C, Ferroni L, Tocco I, Roman M, Munivrana I, Gardin C, Cairns WR, Vindigni V, Azzena B, Barbante C, Zavan B (2013) Active silver nanoparticles for wound healing. Int J Mol Sci 14:4817–4840

Roger JV, Parkinson CV, Choi YW, Speshock JL, Hussain SM (2008) A Preliminary assessment of silver nanoparticle inhibition of monkey-pox virus plciue formation. Nanoscale Res Lett 3:129–133

Rossi-Bergmann B, Pacienza-Lima W, Marcato PD, De-Conti R, Durán N (2012) Therapeutic potential of biogenic silver nanoparticles in murine cutaneous leishmaniasis. J Nano Res 20:89–97

Said DE, Elsamad LM, Gohar YM (2012) Validity of silver, chitosan, and curcumin nanoparticles as anti-*Giardia* agents. Parasitol Res 111:545–554

Salem ANB, Zyed R, Lassoued MA, Nidhal S, Sfar S, Mahjoub A (2012) Plant-derived nanoparticles enhance antiviral activity against coxsakievirus B3 by acting on virus particles and vero cells. Dig J Nanomater Biostruct 7:737–744

Salunkhe RB, Patil SV, Patil CD, Salunke BK (2011) Larvicidal potential of silver nanoparticles synthesized using fungus *Cochliobolus lunatus* against *Aedes aegypti* (Linnaeus, 1762) and *Anopheles stephensi* Liston (Diptera; Culicidae). Parasitol Res 109:823–831

Satyavani K, Gurudeeban S, Ramanathan T, Balasubramanian T (2012) Toxicity study of silver nanoparticles synthesized from *Suaeda monoica* on Hep-2 cell line. Avicenna J Med Biotech 4:35–39

Savithramma N, Rao ML, Rukmini K, Suvarnalatha-Devi P (2011) Antimicrobial activity of silver nanoparticles synthesized by using medicinal plants. Int J Chem Technol Res 3:1394–1402

Seigneuric R, Markey L, Nuyten DSA, Dubernet C, Evelo CTA, Finot E, Garrido C (2010) From nanotechnology to nanomedicine: applications to cancer research. Curr Mol Med 10:640–652

Shameli K, Ahmad MB, Jazayeri SD, Shabanzadeh P, Sangpour P, Jahangirian H, Gharayebi Y (2012) Investigation of antibacterial properties silver nanoparticles prepared via green method. Chem Central J 6:73

Shio MT, Olivier M (2010) Editorial: *Leishmania* survival mechanisms: the role of host phosphatases. J Leukoc Biol 88:1–3

Sondi I, Salopek-Sondi B (2004) Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for gram-negative bacteria. J Colloid Interface Sci 275:177–182

Speshock JL, Murdock RC, Braydich-Stolle LK, Schrand AM, Hussain SM (2010) Interaction of silver nanoparticles with tacaribe virus. J Nanobiotechnol 8:19

Sriram MI, Barath S, Kanth M, Kalishwaralal K, Gurunathan S (2010) Antitumor activity of silver nanoparticles in Dalton's lymphoma ascites tumor model. Int J Nanomed 5:753–762

Su YH, Varhue W, Liao KT, Swami N (2012) Characterizing silver nanoparticle-induced modifications to the dielectric response of Cryptosporidia oocysts. Annual Meeting of the American Electrophoresis Society (AES)

Subarani S, Sabhanayakam S, Kamaraj C (2013) Studies on the impact of biosynthesized silver nanoparticles (AgNPs) in relation to malaria and filariasis vector control against *Anopheles stephensi* liston and *Culex quinquefasciatus* Say (Diptera: Culicidae). Parasitol Res 112:487–499

Sun RW, Chen R, Chung NP, Ho CM, Lin CL, Che CM (2005) Silver nanoparticles fabricated in hepes buffer exhibit cytoprotective activities toward HIV-1 infected cells. Chem Commun 40:5059–5061

Sun L, Singh AK, Vig K, Pillai SR, Singh SR (2008) Silver nanoparticles inhibit replication of respiratory syncytial virus. J Biomed Biotechnol 4:149–158

Tile VA, Bholay AD (2012) Biosynthesis of silver nanoparticles and its antifungal activities. J Environ Res Develop 7:338–345

Trefry JC, Wooley DP (2013) Silver nanoparticles inhibit vaccinia virus infection by preventing viral entry through a macropinocytosis-dependent mechanism. J Biomed Nanotech 9:1624–1635

Xiang DX, Chen Q, Pang L, Zheng CL (2011) Inhibitory effects of silver nanoparticles on H1N1 influenza a virus in vitro. J Virol Methods 178:137–142

Xu Y, Gao C, Li X, He Y, Zhou L, Pang G, Sun S (2013) In vitro antifungal activity of silver nanoparticles against ocular pathogenic filamentous fungi. J Ocul Pharmacol Ther 29:270–274

Zhang H, Smith JA, Oyanedel-Craver V (2012) The effect of natural water conditions on the anti-bacterial performance and stability of silver nanoparticles capped with different polymers. Water Res 46:691–699

Zhang K, Li F, Imazato S, Cheng L, Liu H, Arola DD, Bai Y, Xu HH (2013) Dual antibacterial agents of nano-silver and 12-methacryloyloxydodecylpyridinium bromide in dental adhesive to inhibit caries. J Biomed Mater Res B Appl Biomater 101:929–938