Research Article

Interplays of Nanosilver and Medicinal Domain: Implications and Perspectives

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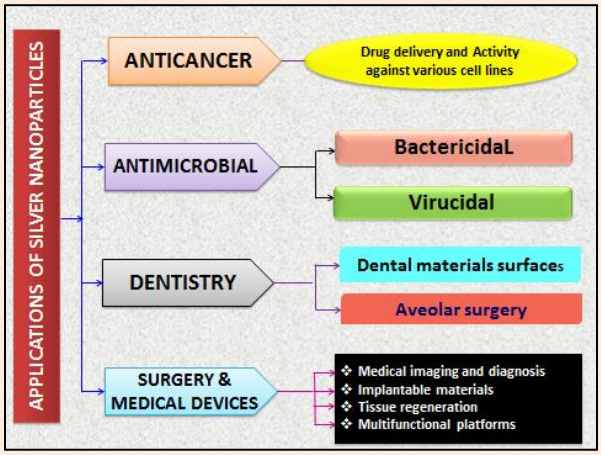
Abstract

Nanotechnology is an escalating field that has made its contribution to all spheres of human life. Silver has been used for millenia in many applications across a diverse range of fields with particular emphasis in therapy and diagnostics. Silver nanoparticles are being utilized in every phase of science along with engineering including medical fields and is still charming scientists to explore new dimensions for their respective worth which is generally attributed to their corresponding small sizes. It is an evolving field having enormous potential to positively impact the environment and health care system. Silver nanotechnology may revolutionize the rules and possibilities of drug discovery and change the landscape of pharmaceutical and biotechnology industries for foreseeable future. The present review explores the huge diversity of to be utilized towards rapid growth with green principles over the conventional ones and describe the biomedical applications of silver nanoparticles.



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Introduction

‘‘There’s plenty of room at the bottom’’ is the title of a lecture in 1959 by Richard Feynman, that introduced the concept of nanotechnology as an important field for future scientific researches [1]. Nanotechnology has finally and firmly entered the realm of drug delivery. Performances of intelligent drug delivery systems are continuously improved with the purpose to maximize therapeutic activity and to minimize undesirable side-effects [2]. Nanotechnology has touched the epitome of miniaturization by integrating various nanometer size particles with nanometer precision. [3] Nanoparticles have become research hot-spot in subjects such as physics, chemistry and materials due to their unique physical and chemical properties [4-10]. Nanosilver particles generally present at 1 to 100 nm in size in at least one dimension. As particle size decreases, the surface area-to-volume ratio of Ag NPs increases dramatically, this leads to significant changes in their physical, chemical, and biological properties [11-14]. Study on metal nanoparticles has been growing dramatically throughout the world in the recent years due to their incredible applications [15]. Nanotechnology, a fast-growing discipline of science, is widespread in various areas of life around the world. One of the examples of nanocompounds is nanosilver, which is used in medicine, electronics, construction industry and chemical technology as an exceptionally efficient antibacterial and antifungal agent [16]. Silver nanoparticles have had a substantial impact across a diverse range of fields such as catalysis [17-19], sensing [20,21], metallic inks [22], therapeutics [23] and medicine [24,25]. Ag NMs have potent antimicrobial properties [26,27] making them suitable for diverse applications. Nanotechnology has evolved as a promising tool in the field of medicine with increasing use of nanoparticles or nanoemulsions for treatment of various diseases [28].

Properties of Ag NPs can be modified by coating shell with functional groups, such as, modulating their solubility [29], self-assembly [30] or allowing selective interactions [31]. Different chromophores have been coupled to Ag NPs

for the design of sensors [32] and as vehicles for tracers and drugs [33]. Interaction of Ag NPs with DNA has been extensively studied for potential applications as smart bio-based nanoparticle assemblies [34], new intercalating agents [35] or gene delivery vectors [36]. Nowadays, extensive efforts have been devoted in developing new classes of powerful antibacterial agents due to the epidemics caused by different pathogenic bacteria. Ag NPs have the ability to interact with various microorganisms (such as bacteria) and also impact both the growth of and mature bacterial biofilms and, therefore, could be used as broad spectrum antimicrobials. The broad spectrum of bioactivity of Ag NPs makes them promising agents not only to fight infections, but in many other biomedical areas. Within this context, nanomaterials have arisen as new promising antimicrobial agents due to their high surface area to volume ratio as well as their unique chemical and physical properties [37]. The potential for the application of Ag NPs in the treatment of diseases is that require maintenance of circulating drug concentration or targeting of specific cells or organs [38]. For example, Ag NPs have been shown to interact with the HIV-1 virus and inhibit its ability to bind host cells in vitro [39]. In this review, we discuss the use of silver in nanotechnology for biomedical applications. Specifically, this review summarizes recent advancements in the application of silver nanotechnology to the therapy of diseases. Clinical trials and future perspective of the use of silver nanocarriers are also discussed. We hope that such a review will be valuable to researchers who are exploring nanosilver drug systems for the treatment of specific diseases.

Cancer

Despite many efforts, cancer is among the top three causes of death in modern society, demanding improved treatments, that currently includes surgery, chemotherapy, and various types of radiation therapy [40,41]. Cancer is the uncontrolled growth of tissues and their rapid invasion without proper development and differentiation [42]. Six biological aptitudes are considered to be 'hallmarks of cancer': proliferative signalling, evasion of growth suppressors, resistance to cell death, replicative immortality, angiogenesis, invasion and metastasis [43]. Conventional cancer therapies face challenges such as poor bioavailability and intrinsic toxicity. The therapeutic efficiency of many useful drugs is compromised by such toxicity issues. Recent technological advances in nanotechnology, molecular biology, and imaging technology allow the application of nanomaterials for early and specific cancer detection and therapy [44]. They are applied in the field of oncology in the same way as in other branches of biomedical nanotechnology [45]. Nanomaterials, such as Ag NPs with their altered pharmacological and therapeutic efficiencies have overcome some of these conventional limitations [46].

Application in breast cancer

Breast cancer is the second leading cancer-related cause of death in women [47] and therefore, significant efforts are being made to develop new, nanotechnology-based therapeutic and diagnostic agents [48,49]. Jeyaraj et. al. have reported the spherical shaped nanoparticles exhibiting promising anticancer property against human breast cancer (MCF-7) cell lines. The Ag NPs induced DNA damage through the generation of reactive oxygen species, suggesting that synthesized Ag NPs will help to find alternative chemotherapeutic agent [50]. Vivek et. al. investigated dose-dependent cytotoxicity green synthesized Ag NPs against human breast cancer cell (MCF-7) and normal breast epithelial cells (HBL-100) and the inhibitory concentration (IC50) were found to be 50 µ/mL, 30 µ/mL, and 80 µ/mL, 60 µ/ml for Ag NPs against MCF-7 and normal HBL-100 cells at 24 h and 48 h incubation respectively. Application of such eco-friendly nanoparticles makes this method potentially exciting for the large scale synthesis of nanoparticles [51].

Sathish kumar et. al. have reported eco-friendly fabrication of colloidal Ag NPs with narrow size range (5–45 nm) and have successfully employed these Ag NPs for biomedical applications. The fabricated Ag NPs showed prominent cytotoxicity effect against human breast carcinoma cells (MCF-7) at minimal dosage (5 lL/mg) [52]. Jannathul et. al. have reported the anticancer potential of plant-mediated silver nanoparticles in vitro, against human breast cancer cell lines MCF-7. The biogenically synthesized Ag NPs embedded with ellagic acid on breast cancer cell lines. The cytotoxic properties of the nanoparticles due to the interaction of nanoparticles with cells and intracellular macromolecules like proteins and DNA [53]. Identification of differential sensitivity of cancer cells as compared to normal cells has the potential to reveal a therapeutic window for the use of Ag NPs as a therapeutic agent for cancer therapy. Swanner et. al. examined the cytotoxicity of Ag NPs in a series of cell lines, including (Triple-negative breast cancer) TNBC [54], luminal A breast cancer, and cell lines derived from noncancerous human breast tissue. They assessed the effects of Ag NPs alone or in combination with ionizing radiation (IR) on DNA damage in vitro and determined the anticancer efficacy of these treatments in a mouse model of TNBC [54].

Application in colon/rectal cancer

Colorectal cancer (CRC) is the third leading cause of cancer death worldwide, and the 5-year relative survival rate is only 8% despite diagnostic and therapeutic advances [63]. Graff et. al. have evaluated the size-dependent effects of Ag NPs by treating the human LoVo colon carcinoma cell line, an intestinal epithelium model, with spherical Ag NPs of well-defined sizes (10, 20, 40, 60 and 100 nm) [64]. Durai et. al. synthesized Ag NPs using sodium para-hydroxybenzoate tetrahydrate (SPHT) i.e. SPHT-Ag NPs inhibit cell proliferation, induces apoptosis and cell cycle arrest against HCT15 and HT29 colon cancer cell lines in vitro. The most potential activity of SPHT-Ag NPs is much in lower concentration. Thus, potential bioactive compound (SPHT) and SPHT-Ag NPs gave promising results on in vivo studies [65]. Prabhu et. al. demonstrated the efficacy of Ag NPs as antitumor agent using human colon cancer cell line HCT15. The results suggested that Ag NPs exerted its antiproliferative effects on colon cancer cell line by suppressing its growth, arresting the G_0/G_1-phase, reducing DNA synthesis and inducing apoptosis [66].

Deeb et. al. investigated the anti-colon cancer activities of the biogenic Ag NPs along with its capping biomolecules *in vitro*. The potentialities of the biogenic Ag NPs against colon cancer proliferation recorded 60% inhibition using its nontoxic dose with a down regulation of the expression of Bcl2 and survivin gene. Ag NPs showed anti-proliferative effects against colon cancer superior to the naked Ag NPs that showed 58.6% inhibition [67]. Sanpui et. al. developed of a chitosan nanocarrier (NC)-based delivery of Ag NPs to mammalian cells for induction of apoptosis at very low concentrations of the NPs. The cytotoxic efficacy of the Ag NP-nanocarrier (Ag-CS NC) system in human colon cancer cells (HT 29) was examined. The NCs elicited the antiproliferative response at a much lower concentration of Ag NPs (330 ng mL^{-1} at IC50). The use of significantly low concentration of Ag NPs impregnated in chitosan nanocarrier is a much superior approach in comparison to the use of free Ag NPs in cancer therapy [69]. Mata et. al. reported the biogenic spherical silver nanoparticles exhibited potent *in vitro* anticancer effects in COLO 205 cells. Ag NPs initiated apoptotic cell death at a very low concentration in COLO 205 (human colon cancer) cells through enhancing intracellular ROS generation and depletion of mitochondrial membrane potential which further cause DNA fragmentation and cell cycle arrest [70]. Arunachalam et. al. showed the anticancer activities of both the bioactive compounds of the leaf extract and the biofunctionalized Ag NPs synthesized against HT29 human adenocarcinoma cells in vitro. In vitro cytotoxic activity of the biofunctionalized green-synthesized Ag NPs indicated that the sensitivity of HT29 human colon adenocarcinoma cells for cytotoxic drugs is higher than that of Vero cell line [71].

Application in lung cancer

Lung cancer is by far the leading cause of cancer-related mortality worldwide, most of them being active tobacco smokers. Non-small cell lung cancer accounts for around 85% to 90% of deaths, whereas the rest is contributed by small cell lung cancer. The extreme lethality of lung cancer arises due to lack of suitable diagnostic procedures for early detection of lung cancer and ineffective conventional therapeutic strategies [72,73].

Mukherjee et. al. have synthesized biocompatible Ag NPs which shows anticancer activity towards different cancer cells including lung cancer as anti-cancer agents. The plausible mechanism includes the formation of reactive oxygen species induced by Ag NPs is one of the plausible mechanisms for the anti-cancer activity [74]. Tynga et. al. synthesized spherical shape of Ag NPs with an average size of 27 nm was able to penetrate and localize A549 cancer cells. This study showed that Ag NPs displayed good photodynamic effects and induced increased cytotoxicity and decreased cell viability and proliferation [75]. Zhou et. al. have synthesized and assessed *in vitro* antiproliferation activities of the spherical shaped silver nanoparticles on human lung cancer cells. Ag NPs inhibited the proliferation of A549 cells following dose and time dependent manner [76]. Han et. al. investigated the toxicity of biologically prepared small size of silver nanoparticles to evaluate the potential toxicity in human lung epithelial adenocarcinoma cells A549. The studies revealed that Ag NPs entered the cell and eventually induced oxidative stress, and oxidative stress could play a role in the formation of autosomes and autolysosomes in A549 cells [77].

Application in leukemia

Leukemias are classified based on the type of white blood cell (myeloid or lymphoid) and the degree of maturity and proliferative tendencies (acute or chronic) of the cell populations involved. The most common leukemias in children are Acute Lymphoblastic Leukemia (ALL) and AcuteMyeloid Leukemia (AML); while ALL is responsible for the majority of pediatric cancer-related deaths [83-85].

Therefore, new approaches are needed to reduce or to avoid off target toxicities, associated with chemotherapy and their long-term residual effects. Recently, nanotechnology has been employed to enhance cancer therapy, via improving the bioavailability and therapeutic efficacy of anti-cancer agents [86]. The cellular uptake and cytotoxic mechanism of Ag NPs in chronic myeloid leukemia (CML) cells were investigated by Guo et. al. Ag NPs entered K562 cells (a chronic myeloid leukemia, CML cell line) in a dose-dependent manner and locate in endosomes. Reactive oxygen species (ROS) generated upon Ag NPs exposure and cause cytotoxicity and apoptosis. Ag NPs treatment inhibited the viability of cells from CML patients [87].

Recently, increased reactive oxygen species (ROS) levels and altered redox status in cancer cells have become a novel therapeutic strategy to improve cancer selectivity over normal cells. It has been known that Ag NPs display anti-leukemic activity via ROS overproduction [88]. Guo et. al. used as a drug model of ROS induction to investigate its synergistic effect with Ag NPs, which exhibited the synergistic anti-leukemia activity with a novel therapeutic drug, N-(4-hydroxyphenyl)retinamide (4-HPR), against mitochondriaand cytoplasm of SHI-1 cells (human acute myeloid leukemia cell line). Ag NPs localized in the mitochondria and induce the overproduction of ROS [89]. Sulaiman et. al. have reported the biomedical potential of silver nanoparticles human acute promyelocytic leukemia (HL-60) cell line. The synthesized silver nanoparticles efficiently reduced the viability of the HL-60 cells in a dose-dependent manner. The mortality data showed that these Ag NPs not only possess of the cytotoxic effect, but also reduce tumors potentially. The cytotoxic effect of silver is because of active physicochemical interaction of silver atoms with the functional groups of intracellular proteins, as well as with the nitrogen bases and phosphate groups in DNA [90]. Thombre et. al. evaluated the role of silver nanoparticles in enhancing the cytotoxic effect of Cyclophosphamide, Mercaptopurine and Busulfan against THP-1 (human acute myeloid leukemia) cell lines [91]. Acute myeloid leukemia (AML) is a clonal disease characterized by the proliferation and accumulation of immature myeloid cells in the bone marrow, which ultimately leads to hematopoietic failure [92]. Guo et. al. demonstrated the polyvinylpyrrolidone (PVP)-coated Ag NPs with various sizes had antileukemia effect against multiple human AML cell lines and primary isolates from AML patients. They have elucidated the cytotoxic effect of Ag NPs on acute myeloid leukemia (AML) cells and their underlying mechanism and that have significant impact on AML treatment. Ag NPs caused the production of reactive oxygen species (ROS), losses of mitochondrial membrane potential (MMP), DNA damage and apoptosis. The cytotoxic effect against AML cells was stronger than that against normal hematopoietic cells [93].

Application in hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the most common and highly malignant cancers in the world. Despite its severity and clinical significance, there is a limited understanding of the pathogenesis. Currently, surgical resection or liver transplantation is effective treatment for early cancers. However, a majority of the liver cancers are diagnosed at a later stage when there are only a few therapeutic options with poor clinical outcome [96]. Loutfy et. al. evaluated cytotoxic effect of Ag NPs on human cucasian hepatocellular carcinoma cell line model (HepG2) and their possible anti-proliferative activity. This new class of engineered nanoparticles with desired physicochemical properties applied as new therapeutic approaches against human liver cancer disease. HepG2 was used as a model of human liver cancer cells. The apoptotic effect was intrinsic apoptotic caspase independent pathway via mitochondrial dysfunction [97]. *Phyllanthus emblica*-Ag NPs were synthesized and ROS generation, apoptotic morphological changes, mitochondrial depolarization, DNA damage and oxidative stress was observed as more in Ag NPs treated cells by Rosarin and co-workers. The results showed that the Ag NPs are capped with biomolecules enhanced cytotoxicity in laryngeal cancer cells through oxidative stress and apoptotic function on Hep2 cancer cells. Cells underwent concentration dependent cytotoxicity by Ag NPs and a significant decrease in the cell viability [98].

Application in oral cancer

Plasmonic nanoparticles (NPs) have become a useful platform in medicine for potential uses in disease diagnosis and treatment [102]. Austin et. al. utilized the plasmonic scattering property and the ability of nuclear-targeted silver nanoparticles (NLS/RGD-Ag NPs) to induce programmed cell death in order to image in real-time the behaviour of human oral squamous carcinoma (HSC-3) cell communities during and after the induction of apoptosis [103]. A poly(lactic-co-glycolic acid) (PLGA)-based uniform (50−100 nm) hybrid Ag NPs with positive zeta potential (0.52 ± 0.09 mV) was prepared by Satapathy et. al. Antitumor activity of Ag NPs was evaluated by using various cancer cell lines including H-357 oral cancer cells and Oral squamous cell carcinoma (OSCC)-cancer stem cell in an in vitro

model system. Ag NPs caused more cytotoxicity in cancer cells than normal epithelial cells. These hybrid Ag NPs not only possess potentiality for cancer cell growth inhibition, but also exhibit anti-CSC efficacy by inhibiting its highly efficient DNA repair machinery as well as angiogenesis [104]. Table 1 summarizes silver nanoparticles developed by different researchers for the determination and treatment of various types of cancer along with their source, size and function of Ag NPs.

Table 1 Treatment of various types of cancer by Ag NPs along with their source, size and function

Type of cancer	Cells	Size (nm)	Source/Method	Function	Reference
Breast cancer	MCF-7	22 -25	*Sesbania grandiflora* leaf extract	Induced apoptosis in the cells. Caused the morphological changes in the cell shape and chromatin condensation.	[50]
	MCF-7	20-100	*Annona squamosa* leaf extract	Induction of apotosis	[51]
	MCF-7	5–45	*Dendrophthoe falcata* leaf extract	AgNPs induced cellular toxicity begin with the cellular uptake of inorganic nanoparticles through clathrin-dependent endocytosis and micropinocytosis.	[52]
	MCF-7	10–30	*Alternanthera sessilis*	Increased level of ROS generation, inhibit the proliferation of MCF-7 cells and caspase cascade-mediated mitochondrial dysfunction.	[53]
	MCF-7, MCF-10A, MDA-MB-231	23–25	Ag NPs capped with polyvinyl pyrrolidone (PVP)	induction of oxidative stress and DNA damage, which can lead to cell death.	[55]
	MDA-MB-231	--	*Acalypha indica* linn	induced apoptosis through caspase-3 activation and DNA fragmentation	[56]
	T47D	< 27	Chemical reduction method	--	[57]
	MDA-MB-231	10-20	Supernatant of *Bacillus funiculus*	Induction of apoptosis in cancer cell line.	[58]
	MCF-7	16-20	Chemical reduction method	Caused apoptotic and necrotic effects in a dose-dependent manner. Induced severe structural damage, accumulate in mitochondria and oxidative stress.	[59]

	MCF-7	28.4	*Couroupita guianensis* leaves	--	[60]
	MCF-7	12-15	*Achillea biebersteinii* flower extract	Caused cytoplasmic condensation, cell shrinkage, aggregation of nuclear chromatin into dense masses and induced DNA fragmentation in cells.	[61]
	MCF-7	--		Induce apoptosis at much lower Ag NP concentration. Increase in reactive oxygen species (ROS) that leads to oxidative stress-induced apoptosis.	[62]
Colon/rectal cancer	LoVo	20-100	--	Generated ROS and inflammatory markers, leading to mitochondrial dysfunction and subsequently inducing apoptosis.	[64]
		26 to 39	*Vitex negundo* Leaves	Induced apoptosis by decreasing cell size, chromatin condensation and nuclear fragmentation due to endonuclease cleavage of DNA	[65]
	HCT15	20-100	*Vitex negundo* leaf extract	Arrested cells at G_0/G_1 and G2/M phases with corresponding decrease in S-phase.	[66]
	Caco 2	12-18	Honey bee extract	Induced cellular apoptosis	[67]
	HCT 116	136-172	Starch	Caused DNA damage, decreased the growth and viability of HCT116 colon cancer cells.	[68]
	HT 29	136.9-172.6	Chitosan	Oxidative stress and mitochondrial dysfunction	[69]
	COLO 205	30 approx.	*Abutilon indicum* leaf extract	Morphological changes, chromatin condensation and membrane potential loss.	[70]
	HT29	--	*Gymnema sylvestre* leaf extract	Induced intracellular reac-tive oxygen species generation and inhibited HT 29 cell proliferation	[71]
Lung cancer	A549	20-60	*Olax scandens* leaf extract	DNA damage induced by ROS and oxidative stress	[74]
	A549	27	--	Induced increased cytotoxicity and	[75]

				decreased cell viability and proliferation	
	A549	15	--	Induced oxidative stress, and oxidative stress could play a role in the formation of autosomes and autolysosomes in cells.	[77]
	A549	--	*Albizia Adianthifolia*	Activated the intrinsic apoptotic pathway	[78]
	A549	--	*Euphorbia nivulia* stem latex	Exhibited gross structural damage and elevated oxidative stress indices.	[79]
	A549	84.00±10.08	*Rosa damascena* petals	Induction of apoptosis activated by caspase 3 enzyme	[80]
	A549	70-100	Citrate reduction method	Caused necrosis and apoptosis in cells.	[81]
	A549	30–50	Ag NPs powder coated with 0.2% PVP (poly vinyl pyrrolidone)	DNA damage induced by ROS and mitochondrial damage	[82]
Leukemia	K562	--	Polyol method	Cell cycle status and several critical regulators alteration	[87]
	SHI-1 check cell line	11.17 ± 0.62	Electrochemical method	Induced apoptosis via overproduction of ROS	[89]
	HL-60	30	Chemical reduction method	Inactivation of DNA replication, inhibition of enzyme functions which results in loss of cell viability and eventually resulting in cell death	[90]
	THP -1	17-20	*Bacillus subtilis* Biophysical method	Disruption of the mitochondrial respiratory chain. Reactive Oxygen Species and disturbance of ATP synthesis and thus, DNA damage	[91]
					[93]
	HL-60	4.7 and 42	--	Oxidative stress and ROS production	[94]
	THP-1	20-25	Reduction method	DNA damage	[95]
Hepatic cancer	HepG2	22	Chemical reduction method	DNA fragmentation, mitochondrial dysfunction and ROS production	[97]

	Hep2		*Phyllanthus emblica*	Induced ROS generation, apoptotic morphological changes, mitochondrial depolarization, DNA damage and oxidative stress.	[98]
	C3A	20	--	Oxidative stress	[99]
	HepG2	10-50	Dried mint leaves	decrease production of reactive oxygen species (ROS), cycle arrest in the G2/M phase and sub G1 stage. interruption of ATP synthesis and induced apoptosis	[100]
	HepG2	16-32	*Premna serratifolia* leaf extract		[101]
Oral cancer	H-357	50-100	Single emulsion solvent evaporation method	Caused apoptosis by inhibiting the angiogenesis	[104]
	HSC-3	35	See agin in paper from ref. no.	Caused DNA damage and apoptotic populations in cancer cells.	[103]

Medical devices

Device-associated infection (DAI) remains a challenge to modern medicine as more patients are being implanted with medical devices that provide surfaces and microenvironments for bacterial colonization [105]. The combined use of both silver nanoparticles and magnetic beads to demonstrate the potential utility of an electrochemical approach for silver dissolution and quantification that could provide a platform technology for a range of point of care and other diagnostic devices [106]. Medical device associated infections are a persistent medical problem which has not found a comprehensive solution yet. Over the last decades, there have been intense research efforts toward developing antibacterial coatings that could potentially improve medical outcomes. Silver nanoparticles have attracted a great deal of attention as a potent alternative to conventional antibiotics. Taheri et. al. have presented a facile approach for the generation of biologically inspired antibacterial coatings with anti-inflammatory properties. A synthetic process for the synthesis of lipid bilayer encapsulated silver nanoparticles was developed for first time. The coatings showed excellent capacity to control bacterial colonization and biofilm formation as the growth of *S. aureus* and *P. aeruginosa* was reduced by 70% and 80%, respectively, while colonization by *S. epidermidis* was almost completely inhibited. The combination of excellent antibacterial properties and the potential to reduce inflammation make the coatings presented in this article a good candidate for the application on medical devices such as wound dressings and catheters [107].

Biofilm formation on in dwelling medical devices and implants such catheters, mechanical heart valves, pacemakers, prosthetic joints, and contact lenses pose a critical medical problems. Biofilm formation by human bacterial pathogens on implanted medical devices causes major morbidity and mortality among patients, and leads to billions of dollars in healthcare cost [108]. Eby et. al. reported a method for the synthesis of antimicrobial coatings on medical instruments that combines the bacteriolytic activity of lysozyme and the biocidal properties of silver nanoparticles. Colloidal suspensions of lysozyme and silver nanoparticles were electrophoretically deposited onto the surface of stainless steel surgical blades and needles. Electrodeposited films firmly adhered to stainless steel surfaces even after extensive washing and retained the hydrolytic properties of lysozyme [109]. Different approaches have been used for preventing biofilm-related infections in health care settings. Many of these methods have their own de-merits, which include chemical-based complications; emergent antibiotic resistant strains, etc. The formation of biofilm is the hallmark characteristic of *Staphylococcus aureus* and *S. epidermidis* infection, which consists of

multiple layers of bacteria encased within an exopolysachharide glycocalyx. Ansari et. al. demonstrated the biofilm formation by methicillin resistance S. aureus (MRSA) and methicillin resistance *S. epidermidis* (MRSE) isolated from wounds. The Ag NPs coated surfaces effectively restricted biofilm formation of the tested bacteria. The Ag NPs prevented formation of the coating on medical devices due to highly antibiotic resistant biofilm [110].

In particular, bacteria are commonly found to adhere more preferably to hydrophobic materials and many of which are used to make medical devices. There is an urgent need to find alternatives to antibiotics in the prevention and treatment of device-associated infections world-wide. Silver nanoparticles have emerged as a promising non-drug antimicrobial agent which has shown effectiveness against a wide range of both Gram-negative and Gram-positive pathogen. Tran et. al. impregnated the hydrophobic polycaprolactone (PCL) polymer, which is a FDA-approved polymeric medical device material, with hydrophilic silver nanoparticles to enhance antimicrobial efficacy [111]. Polymethylmethacrylate **(**PMMA) thin films doped with Ag NPs and silver–imidazole helical complexes (Ag Im) were studied by Lyutakov et. al. . AgIm and Ag NPs doped films showed more stable antimicrobial properties. PMMA films doped with Ag^+ had greater activity than those doped with nanoparticles and silver–imidazole polymeric complexes [112]. Infections associated with medical devices cause significant costs, morbidity, and mortality. Medical devices with hemocompatibility, antioxidative stress, and antibacterial properties are difficult to fabricate. Ag NPs were synthesized in the presence of carboxylic carboxylic D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS) for the first time. The Ag NP-loaded polypropylene (PP) membranes had excellent hemocompatibility for resisting platelet adhesion. The Ag NPs loaded on the surface prevented bacterial adhesion during the early stages and inhibited the formation of biofilms [113]. Implantable devices are major risk factors for hospital-acquired infection. In this field, Furno et. al. developed a completely new approach using supercritical carbon dioxide to impregnate silicone with nanoparticulate silver metal in biomaterials [114].

Dentistry

Nanotechnology offers the opportunity to ameliorate preventive dentistry by directly influencing the process of bacterial adhesion, biofilm formation, and biomineralization on the nanoscale level. These innovative strategies are based on biomimetic as well as bioinspired approaches or on purely artificial nanoparticles [115]. Nanotechnology has been used for medical applications in several forms, including dental practice with the development of Ag NPs as a useful tool in dental practice. Silver compounds and NPs have already been used as dental restorative material, endodontic retrofill cements, dental implants and caries inhibitory solution [116]. In dentistry, both restorative materials and oral bacteria are believed to be responsible for restoration failure. Secondary caries is found to be the main reason to restoration failure. Secondary caries is primarily caused by invasion of plaque bacteria (acid-producing bacteria) such as *Streptococcus mutans* and lactobacilli in the presence of fermentable carbohydrates. To make long-lasting restorations, antibacterial materials should be made [117]. Three different sizes of silver nanoparticles (9.3, 21.3 and 98 nm) were prepared, characterized and an adherence testing was performed to evaluate their anti-adherence activity on a reference strain of *S. mutans* on healthy dental enamel surfaces. Silver nanoparticles showed an adherence inhibition on *S. mutans* and the anti-adherence capacity was better when silver nanoparticles were smaller [118].

Xu et. al. developed the first-generation of bioactive nanocomposites and nanostructured bonding agents with antibacterial and remineralizing capabilities. Nanoparticles of amorphous calcium phosphate (NACP) and Ag NPs and quaternary ammonium dimethacrylate (QADM) were synthesized and incorporated into composites and adhesives. Specimens were inoculated with biofilms. The agents reduced lactic acid and (colony forming unit) CFU of total microorganisms, total streptococci, and mutans streptococci by an order of magnitude, without adversely affecting dentin bond strength [119]. Melo et. al. incorporated Ag NPs and nanoparticles of amorphous calcium phosphate (NACP) into adhesive for the first time and investigated the effects on dentin bond strength and plaque microcosm biofilms. Ag NPs in bonding agents greatly reduced the biofilm viability and metabolic activity, compared to the control. Dental plaque microcosm biofilm viability and acid production were greatly reduced on bonding agents containing Ag NPs and nanoparticles of amorphous calcium phosphate (NACP), without compromising dentin bond strength. The method of incorporating dual agents (remineralizing agent NACP and antibacterial agent Ag NPs) is applicable to other dental bonding systems also [120]. Magalhaes et. al. evaluated the antibacterial activity of three dental cements modified by nanosilver against *S. mutans* [121]. Resin composites, as most popular dental restorative materials, possess excellent properties such as: good esthetic properties, acceptable mechanical properties, fast restoration, etc. [122]. Liu et. al. investigated the effect of trace addition of oleic acid coated Ag nanocrystals (Ag NCs) on mechanical and antibacterial properties of dental resin composites. The antibacterial test demonstrated that

trace Ag NCs provided the resin composites with an antibacterial effect. Such strong and antibacterial dental resin composites are advantageous to prevent secondary caries and be potential for future clinical applications [123]. Miresmaeili et. al. have evaluated the effect of nanosilver incorporation on antibacterial properties and Bracket Bond Strength (BBS) of orthodontic composite resin. Antibacterial activity was determined by evaluation of bacterial growth in suspension media versus growth in direct contact with specimens. BBS and bond failure interface (ARI) were evaluated and compared between the specimens. Nanosilver containing composite could confer surface antibacterial activity without significant difference on BBS and ARI [124]. Antibacterial bonding agents are promising to hinder the residual and invading bacteria at the tooth–restoration interfaces. Zhang et. al. developed an antibacterial bonding agent by incorporation of quaternary ammonium dimethacrylate (QADM) and Ag NPs and to investigate the effect of QADM-Ag NPs adhesive and primer on dentin bond strength and plaque microcosm biofilm. Human saliva as inoculum was used to investigate biofilm metabolic activity, colony-forming unit (CFU) counts, lactic acid production, and live/dead staining assay (n = 6). Adding QADM and NAg in both adhesive and primer had the strongest antibacterial activity, reducing metabolic activity, CFU and lactic acid by an order of magnitude, compared to control [125].

Bactericidal activity

Recently, resistance to commercially available antimicrobial agents by pathogenic bacteria and fungi is increasing at an alarming rate and has become a global threat. Drug resistance is one of the most serious and widespread problems in all developing countries [126]. Despite the current advancement in drug discovery and pharmaceutical biotechnology, infection diseases induced by bacteria continue to be one of the greatest health problems worldwide, afflicting millions of people annually. Almost all microorganisms have, in fact, an intrinsic outstanding ability to flout many therapeutic interventions, thanks to their fast and easy-to-occur evolutionary genetic mechanisms. Silver nanoparticles as biocides tend to target multiple sites on or within bacterial cells and hence have a broad spectrum activity [127,128]. There is an urgent need for alternatives to antibiotics in preventing and treating these infections as a result of increases in drug resistance. The capacity of Ag NPs to destroy infectious micro-organisms makes it one of the most powerful antimicrobial agents, an attractive feature against 'super-bugs' resistant to antibiotics. Silver nanoparticles (Ag NPs) have been incorporated into commercial products at a growing rate in recent years. Their broad application primarily stems from their potent antimicrobial properties [129]. Ag NPs have emerged as a promising non-antibiotic antimicrobial agent against a wide range of bacteria. The increased emergence of drug resistant microbes creates a major challenge to the scientific community for successful development of effective therapeutics. The antimicrobial activities of nanosilver are well known. S. Mohanty et. al. have evaluated the antibacterial effects of Ag NPs against different human pathogens representing Gram-positive, Gram-negative, and acid-fast bacteria. Ag NPs exhibit potent antibacterial activity, impede biofilm formation and kill intracellular mycobacteria. The Ag NPs are potential template for designing of antibacterial agents to target bacterial colonization and to overcome drug resistance [130]. In-vitro antibacterial study of the prepared nanoparticles on different Gram negative (*Staphylococcus aureus and Bacillus subtilis)* and Gram positive bacteria (*Escherichia hermanii*, and *Pseudomonas aeruginoss*) was carried out by Prusty et. al. [131].

Vibrio cholerae and enterotoxic Escherichia coli remain two dominant bacterial causes of severe secretory diarrhoea and still a significant cause of death, especially in developing countries. The Ag NPs has significantly reduced the colonization rates of the pathogens by 75- or 100-fold, respectively [132]. Rajakannu et. al. used simple approach for the biosynthesis of Ag NPs by using aqueous extract of the fruits of *Garcinia mangostana*. The biosynthesized Ag NPs have antibacterial activity against three human pathogens such as *Escherchia coli, Pseudomonas auroginosa* and *Staphylococcus aureus*. The mechanism of action includes membrane interacting ability and functional modulating nature of Ag NPs. Ag NPs attach to the surface of the cell membrane, disturbs its function and penetrates directly with the bacterial outer membrane and releases Ag ions [133]. Synergistic antimicrobial potential of silver nanoparticles has been evaluated with various commercial antibiotics against Gram positive (*Staphylococcus aureus* and *Bacillus cereus*) and Gram negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria by Padalia and co-workers by a simple and eco-friendly route [134]. Pasha et. al. investigated reports facile fabrication of silver nanoparticles from endophytic fungi assessed their antibacterial activity against ***E.*** *coli, S. typhi, B. subtilis* and *S. aureus.* Ag NPs showed deformed and damage of DNA [135]. Velmurugan et. al. have reported antibacterial activity of photosynthesized Ag NPs against skin pathogens *Propionibacterium acnes* and *Staphylococcus epidermidis* compared with commercial Ag NPs. The Ag NPs exhibited antibacterial activity against both bacteria and DNA proteins by interacting with the microbial cell wall or plasma membrane [136]. To provide a

larger overview of the antibacterial activity of Ag NPs, a consolidated summary of major bacteria removed and treated by Ag NPs are outlined in Table 2.

Table 2 Summary of antimicrobial activities of Ag NPs on various target organisms

Source/method of synthesis of Ag NPs	Target organisms	References
Eichhornia crassipes leave extract	*Staphylococcus aureus, Bacillus subtilis, Escherichia hermanii, Pseudomonas aeruginoss*	[131]
Caltropis procera fruit or leaves	*Vibrio cholera, escherichia coli*	[132]
Garcinia mangostana fruit extract	*Escherchia coli, Pseudomonas auroginosa, staphylococcus aureus*	[133]
Tagetes erecta plant extract	*Staphylococcus aureus, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa*	[134]
Colletotrichum sp. ALF2-6	*Escherichia coli, salmonella typhi, , Bacillus subtilis, Staphylococcus aureus*	[135]
Prunus yedoensis leave extract	*Propionibacterium acnes, Staphylococcus epidermidis*	[136]
Curcumin	*Escherichia. coli, Staphylococcus aureus*	[137]
Reduction method	*Escherichia coli, Staphylococcus aureus*	[138]
Reduction method	*Escherichia. coli, Staphylococcus aureus*	[28]
Ocimum tenuiflorum, Solanum tricobatum, Syzygium cumini, Centella asiatica and *Citrus sinensis* plant extract	*Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*	[139]
Reduction method	*Escherichia coli, Staphylococcus aureus*	[140]
Reduction method	*Escherichia coli, Staphylococcus aureus*	[141]
Condensation method	*Escherichia coli, Staphylococcus aureus*	[142]
Sesamum indicum seed extract	*Staphylococcus epidermidis and salmonella typhi*	[143]
Glutathione	*Escherichia coli, Staphylococcus aureus*	[25]
Chlorella pyrenoidosa	*Klebsiella pneumoniae, Aeromonas hydrophila, Staphylococcus aureus*	[144]
Chemical method	*Bacillus cereus, Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia*	[145]
Torreya nucifera	*Salmonella typhimurium*	[146]
Olive leaf extract	*Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli*	[147]
Amphora-46	*Escherichia coli, bacteria Bacillus Stearothermophilus, Streptococcus mutans*	[148]
Azadirachta indica leaves	*Klebsiella pnuemoniae, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans*	[149]
Pterocarpus santalinus leaf extract	*Staphylococcus aureus, Streptococcus Pneumoniae*	[150]
Reduction method	*Escherichia coli, Bacillus subtilis*	[151]

Virucidal activity

In modern era, viral infections constitute one of the main health problems. Chemically synthesized antiviral drugs have adverse side effects which are associated with other health complications. Ag NPs have been shown to inhibit viruses including Human immunodeficiency virus 1 (HIV-1), Hepatitis B virus and Influenza virus. Despite large gaps of knowledge regarding the mechanism, studies indicate that Ag NPs act early in the viral replication cycle [152,153]. The antimicrobial activities of Ag NPs against viruses such as HIV-1 [154], hepatitis B [155], herpes simplex [156], respiratory syncytial [157], monkeypox [158] and H1N1 influenza A virus [159,160] have also been investigated by researchers. The interaction of nanoparticles with biomolecules and microorganisms is an expanding field of research. Within this field, an area that has been largely unexplored is the interaction of metal nanoparticles with viruses. Luis et. al. demonstrated that silver nanoparticles undergo a size dependent interaction with HIV-1, with nanoparticles exclusively in the range of 1–10 nm attached to the virus. Ag NPs interact with the HIV-1 virus via preferential binding to the gp120 glycoprotein knobs. Due to this interaction, silver nanoparticles inhibit the virus from binding to host cells [161].

Virus infections pose significant global health challenges, especially in view of the fact that the emergence of resistant viral strains and the adverse side effects associated with prolonged use continue to slow down the application of effective antiviral therapies. Silver particles in each preparation exhibited a tendency to bind with to the 120 glycoprotein knobs, effectively blocking the binding with host cells. This research demonstrated a dose-dependent and a size dependent interaction of silver nanoparticles with HIV [162]. Current emphasis on elimination of the HIV/AIDS epidemic challenges researchers to assess the efficacy of Ag NPs alternative treatment modalities. Lara et. al. concluded that the antiviral activity of Ag NPs results from their inhibition of the interaction between gp120 and the target cell membrane receptors. Antiviral action allows silver nanoparticles to inhibit HIV-1 infection regardless of viral tropism or resistance profile, to bind to glycoprotein (gp120) in a manner that prevents CD4-dependent virion binding, fusion, and infectivity, and to block HIV-1 cell-free and cell-associated infection, acting as a virucidal agent. The Ag NPs inactivated HIV particles in a short period of time, exerting their activity at an early stage of viral replication (entry or fusion) and at postentry stages [163].

Influenza is a human and animal health problem and an acute respiratory disease caused by the influenza virus and spreads around the world in seasonal epidemics. It is generally spread through the air by coughs, sneezes, and direct contact with the contaminated materials such as body fluids [164]. The pathogen is responsible for 3–5 million severe cases of illness and the influenza virus shows a high variability because of the antigenic shifts in different species and antigenic drifts arising from mutations of the genome [165]. Silver nanoparticles have demonstrated efficient inhibitory activities against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). However, the effects of silver nanoparticles against H1N1 influenza A virus remain unexplored. In this perspective, the interaction of silver nanoparticles with H1N1 influenza A virus has been investigated by Xiang et. al. The Ag NPs were active against H1N1 influenza A virus which is responsible commonly for infection. These Ag NPs provided enhanced protection against influenza virus infection without the risk of cell toxicity [166]. Ag NPs/chitosan (Ch) composites with antiviral activity against H1N1 influenza A virus were prepared. Size dependence of the Ag NPs on antiviral activity was also observed: antiviral activity was generally stronger with smaller Ag NPs in the composites [167]. Nanoparticles have been extensively studied as potential antimicrobials to target pathogenic and multi-drug resistant microorganisms. Their applications recently extended to development of antivirals to inhibit viral infections by Fatima et. al. The synthesized silver nanoparticles using Cinnamomum cassia (Cinnamon) and evaluated their activity against highly pathogenic avian influenza virus subtype H7N3. The silver nanoparticles derived from Cinnamon extract enhanced the antiviral activity and were found to be effective in both treatments, when incubated with the virus prior to infection and introduced to cells after infection [168]. The interaction between silver nanoparticles and viruses is attracting great interest due to the potential antiviral activity of these particles, and is the subject of much research effort in the treatment of infectious diseases. Gaikwad et. al. demonstrated that silver nanoparticles undergo a size-dependent interaction with herpes simplex virus types 1 and 2 and with human parainfluenza virus type 3. The Ag NPs reduced viral infectivity by blocking interaction of the virus with the cell, depending on the size and zeta potential of the silver nanoparticles. Smaller-sized nanoparticles inhibit the infectivity of the viruses analysed [169].

The herpes simplex virus 2 (HSV-2) is one of the most important sexually transmitted pathogens, and can facilitate the spread of human immunodeficiency virus. The currently available antiviral drugs have certain limitations. Nanosilver has received increasing attention recently with respect to its antibacterial and antiviral

properties. Hu et. al. proposed inhibiting effect and mechanism of silver nanoparticles (Ag-NPs) on HSV-2. The cytotoxicity of Vero cells induced by different Ag-NP concentrations was investigated. The mixture of Ag NPs suspension and HSV-2 prior to infecting cells could significantly inhibit the production of progeny viruses. Ag NPs also inhibited the replication of HSV-2 for 24 h before infecting cells with HSV-2 [170]. The interaction between silver nanoparticles and herpesviruses is attracting great interest due to their antiviral activity and possibility to use as microbicides for oral and anogenital herpes. Orlowski et. al. demonstrated that tannic acid modified silver nanoparticles sized 13 nm, 33 nm and 46 nm are capable of reducing HSV-2 infectivity both in vitro and in vivo. Ag NPs induced production of cytokines and chemokines important for anti-viral response. Ag NPs can be used not only as a microbicide to treat HSV-2 infections of the anogenital area, but also to treat oral herpes infections in the form of a protective gel or cream to be applied topically [171].

Perspective and Conclusions

This review presented a comprehensive summary on applications of nanosilver based labels in recent years. The insights provided in this review are important for enhancing the understanding the highly suitable properties of silver nanoparticles in diverse fields of medicine and imaging. We have tried to bring together the results related to the interaction of silver and its compounds with living cells, giving an integrating view from the materials via the microscopic to the molecular scale. The potential benefits of nanotechnology in biomedical and industrial applications have become widely accepted and are the most promising sector for the generation of new applications in medicine. Silver nanotechnology has received significant attention from scientists in the past few decades, raising hopes of revolutionary developments in a wide range of technologies. This review summarizes the medicinal progress in the area of Ag NPs. Ag NPs have exhibited significantly distinct and unique optical, electrical, and biological properties that have attracted attention because of their potential uses in numerous applications. The high efficiency of Ag NPs has been proven to be important mainly because of their antimicrobial properties. Thus, various studies have further investigated the mechanistic aspects of anticancer, antiviral and their applications in the field of dentistry and surgery also. It is now clear that Ag NPs possess a strong antibacterial and antiviral activity, highlighted by several studies.

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Abbreviations

Silver nanoparticles (Ag NPs)
Silver nanomaterials (Ag NMs)
Nano composites (NCs)
Nano carrier (NC)
Nanopartoicles (NPs)
Reactive oxygen species (ROS)
Sodium para-hydroxybenzoate tetrahydrate (SPHT)
Acute Lymphoblastic Leukemia (ALL)
AcuteMyeloid Leukemia (AML)
N-(4-hydroxyphenyl)retinamide (4-HPR)
Mitochondrial membrane potential (MMP)
Polypropylene (PP)
D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS)
Polymethylmethacrylate (PMMA)
Nanoparticles of amorphous calcium phosphate (NACP)
Quaternary ammonium dimethacrylate (QADM)
Colony forming unit (CFU)
Human immunodeficiency virus (HIV)
Hepatitis B virus (HBV)
Chitosan (Ch)
Herpes simplex virus 2 (HSV-2)

References

[1] R. Feynman, *California Institute of Technology, USA*, 1960.
[2] J. Safari, Z. Zarnegar, *J Saudi Chem Soc.*, 2014, 18, 85.
A. Samanta, S. Banerjee, Y. Liu, *Nanoscale*, 2015, 7, 2210.
[3] J. Ke, J.-W. Xiao, W. Zhu, H. Liu, R. Si, Y.-W. Zhang, C.-H. Yan, *J. Am. Chem. Soc.*, 2013,135, 15191.
[4] S. Zhang, L. Nguyen, Y. Zhu, S. Zhan, C. Tsung, F. Tao, *Acc. Chem. Res*, 2013, 46, 1731.
[5] S. Dutta, C. Ray, S. Sarkar, M. Pradhan, Y. Negishi, T. Pal, *ACS Appl. Mater. Interfaces,* 2013, 5, 8724.
[6] P. V. kumar, A. Ramdass, S. Rajagopal, *J. Nanosci. Nanotechnol.*,2013, 13, 7, 4761.
[7] N. J. Borys, E. Shafran, J. M. Lupton, *Sci. Rep.*, 2013, 3, 2090.
[8] B. Nowack, H. F. Krug, M. Height, *Environ. Sci. Tech.*, 2011, 45, 1177.
[9] S. Ramyaa, T. Shanmugasundarama, R. Balagurunathan, *J. Trace Elem. Med. Biol.*, 2015, 32, 30.
[10] J. Chen, J. Ouyang, J. Kong, W. Zhong, M. M. Xing, *ACS Appl. Mater. Interfaces,* 2013, 5(8), 3108.
[11] Mohamed, M. M. Xing, *Int. J. Burns Trauma,* 2012, 2(1), 29.
[12] Y. Tian, J. Chen, F. Zahtabi, R. Keijzer, M. Xing, *Pediatr. Pulmonol.*, 2013, 48, 1098.
[13] M. Xing M, W. Zhong, X. Xu, D. Thomson, *Langmuir,* 2010, 26, 11809.
[14] S. Priyadarshini, V. Gopinath, N. M. Priyadharsshini, D. M. Ali, P. Velusam, *Colloids Surf. B Biointerfaces*, 2013, 102, 232.
[15] J. Pulit, M. Banach, Z. Kowalski, *Ecol. Chem. Eng. S*, 2011, 18, 185.
[16] A. Bayat, M. Shakourian-Fard, N. Ehyaei, M. M. Hashemi, *RSC Adv.*, 2015, 5, 22503.
[17] P. Khoza, T. Nyokong, *J. Mol. Catal.*, 2015, 399, 25.
[18] P. Christopher, H. Xin, S. Linic, *Nat. Chem.*, 2011, 3, 467.
[19] P. Khoza, T. Nyokong, *J. Mol. Catal.*, 2015, 39, 25.
[20] V. V. Kumar, S. P. Anthony, *RSC Adv.*, 2014, 4, 18467.
[21] E. Comini , C. Baratto , I. Concina , G. Faglia , M. Falasconi , M. Ferroni , V. Galstyan, E. Gobbi, A. Ponzoni, A. Vomiero, D. Zappa, V. Sberveglieri, G. Sberveglieri, *Sensors Actuat. B*, 2013, 179, 3.
[22] S. Shrivastava, T. Bera, S.K. Singh, G. Singh, P. Ramachandrarao, D. Dash, *ACS Nano,* 2009, 3, 1357.
[23] E. P. Hoppmann, W. W. Yu, I. M. White, *Methods*, 2013, 63, 219.
[24] A. Taglietti, Y. A. Diaz Fernandez, E. Amato, L. Cucca, G. Dacarro, P. Grisoli, V. Necchi, P. Pallavicini, L. Pasotti, M. Patrini, *Langmuir*, 2012, 28, 8140.
[25] D. Singh, N. Barman, K. Sahu, *J. Colloid Interface Sci.*, 2014, 413, 37.
[26] M. Liong, B. France, K.A. Bradley, J. I. Zink, *Adv. Mat.*, 2009, 21, 1684.
[27] J. S. Kim, E. Kuk, K. N. Yu, J. H. Kim, S. J. Park, H.J. Lee, *Nanomed.*, 2007, 3, 95.
A. Kanaras, F. S. Kamounah, K. Schaumburg, C. J. Kiely, M. Brust, *Chem.Comm.*, 2002, 2294.
[28] P. Alivisatos, K. P. Johnsson, X. Peng, T. E. Wilson, C. J. Loweth, M. Bruchez, P. J. Schultz, *Nature*, 1996, 382, 609.
[29] X. Li, J. Wang, L. Sun, Z. Wang, *Chem.Comm.*, 2010, 46, 988.
[30] S. Ribrioux, G. Kleymann, W. Haase, K. Heitmann, K. Ostermeier, H. J. Michel, *J. Histochem. Cytochem.*, 2007, 44, 207.
[31] U. H. F. Bunz, V. M. Rotello, *Angew. Chem. Int. Ed. Engl.*, 2010, 49, 3268.
[32] A. P. Alivisatos, K. P. Johnsson, X. Peng, T. E. Wilson, C. J. Loweth, M. Bruchez, P. J. Schultz, *Nature*, 1996, 382, 609.
[33] G. Wang, J. I. Zhang, R. W. Murray, *Anal. Chem.*, 2002, 74, 4320.
[34] A. K. Boal, F. Ilhan, J. E. Derouchey, T. Thurn-Albrecht, T. P. Russell, V. M. Rotello, *Nature*, 2000, 404, 746.
[35] M. Rai, A. Yadav, A. Gade, *Biotech. Adv.*, 2009, 27, 76.
[36] J. Panyam, V. Labhasetwar, *Adv Drug Deliv Rev,* vol. 55, pp. 329–47. 2003.
[37] J. L. Elechiguerra, J. Burt, J. R. Morones, *J. Nanobiotech.*, 2005, 3, 6.

[38] Y. Liu, H. Miyoshi, M. Nakamura, *Int. J. Cancer*, 2007, 120, 2527.
[39] National Cancer Institute, *Breast Cancer Treatment*, 2007, http://www.cancer.gov.
[40] S. Nazir, T. Hussain, A. Ayub, U. Rashid, A. J. MacRobert, *Nanomedicine*, 2014, 10, 19.
[41] D. Hanahan, R. A. Weinberg, *Cell*, 2011, 144, 646.
[42] B. Blasiak, F. C. J. M. Veggel, B. Tomanek, *J. Nanomat.*, 2013, 1.
[43] N. Ahmed, H. Fessi, A. Elaissari, *Drug Discov.Today*, 2012, 17, 928.
[44] S. Y. Clarence, G. S. Simate, *Int. J. Pharm.*, 2015, DOI10.1186/s40199-015-0125-6.
[45] A. T. Toriola, G. A. Colditz, *Breast Cancer Res.*, 2013, 138, 665.
[46] E. K. H. Chow, D. Ho, *Sci. Transl. Med.*, 2013,DOI: 10.1126/scitranslmed.3005872.
[47] S. Bhattacharyya, R. A. Kudgus, R. Bhattacharya, P. Mukherjee, *Pharm. Res.*, 2011, 28, 237.
[48] M. Jeyaraj, G. Sathishkumar, G. Sivanandhan, D. MubarakAli, M. Rajesh, R. Arun, G.
[49] Kapildev, M. Manickavasagam, N. Thajuddin, K. Premkumar, A. Ganapathi, *Colloids Surf B Biointerfaces*, 2013, 106, 86.
[50] R. Vivek, R. Thangama, K. Muthuchelian, P. Gunasekaran, K. Kaveri, S. Kannan, *Process Biochem.*, 2012, 47, 2405.
[51] G. Sathishkumar, C. Gobinath, A. Wilson, S. Sivaramakrishnan, *Spectrochim. Acta Mol. Biomol.*, 2014, 128, 285.
[52] M. J. Firdhouse, P. Lalitha, *Prog. Biomat.*, 2015, 4, 113.
[53] I. A. Mayer, V. G. Abramson, B. D. Lehmann, J. A. Pietenpol, *Clin. Cancer Res.*, 2014, 20, 782.
[54] J. Swanner, J. Mims, D. L. Carroll, S. A. Akman, C. M. Furdui, S. V Torti, R. N. Singh, *Int. J. Nanomed.*, 2015, 10, 3937.
[55] C. Krishnaraj, P. Muthukumara, R. Ramachandran, M. D. Balakumaran, P. T. Kalaichelvan, *Biotech. Rep.*, 2014, 4, 42.
[56] S. N. Ostad, S. Dehna, Z. E. Nazari, S. T. Fini, N. Mokhtari, M. Shakibaie, A. R. Shahverdi, *J. Med. Biotech.*, 2010, 2, 187.
[57] S. Gurunathan, J. W. Han, V. Eppakayala, M. Jeyaraj, J.-H. Kim, *BioMed Research International*, 2013, http://dx.doi.org/10.1155/2013/535796.
[58] H. Çiftci, M. Turk, U. Tamer, S. Karahan, Y. Menemen, *Turk. J. Bio.*, 2013, 37, 573.
[59] P. Devaraj, P. Kumari, C. Aarti, A. Renganathan, *J. Nanotech.*, 2013, http://dx.doi.org/10.1155/2013/598328.
[60] J. Baharara, F. Namvar, T. Ramezani, M. Mousavi, R. Mohamad, *Molecules*, 2015, 20, 2693.
[61] B. Bhushan, P. Gopinath, *RSC Adv.*, 2015, 5, 86242.
[62] E. N. G.-Treviño, S. L. S.-Fernández, H. G. M.-Rodríguez, *Cancer Cell Int.*, 2015, DOI 10.1186/s12935-015-0163-7, 2015.
[63] R. M.-Graff, R. Rumpker, M. Richter, T. V.-Braga, F. Kjeldsen, J. Brewer, J. Hoyland, H.-G. Rubahn, H. Erdmann, *Toxic. Vitro*, 2014, 28, 1280.
[64] P. Dura, A. Chinnasamy, B. Gajendran, M. Ramar, S. Pappu, G. Kasivelu, A. Thirunavukkarasu, *Eur. J. Med. Chem.*, vol. 84, pp. 90-99, 2014.
[65] D. Prabhu, C. Arulvasu, G. Babu, R. Manikandan, P. Srinivasan, *Process Biochem.*, 2013, 48, 317.
[66] N. M. El-Deeb1, I. M El-Sherbiny, M. R. El-Aassara, E. E. Hafez, *J. Nanomed. Nanotech.*, 2015, http://dx.doi.org/10.4172/2157-7439.1000265.
[67] S. R. Satapathy, P. Mohapatra, R. Preet, D. Das, B. Sarkar, T. Choudhuri, M. D. Wyatt, N. Kundu, *Nanomedicine*, 2013, 8, 1307.
[68] P. Sanpui, A. Chattopadhyay, S. S. Ghosh, *ACS Appl. Mat. Interfaces.* 2011, 3, 218.
[69] R. Mata, J. R. Nakkala, S. R. Sadras, *Colloids Surf. B: Biointerfaces*, 2015, http://dx.doi.org/doi:10.1016/j.colsurfb.2015.01.052.
[70] K. D. Arunachalam, L. B. Arun, S. K.. Annamalai and A. M. Arunachalam, *Int. J. Nanomed.*, 2015, 10, 31.
[71] U. K. Sukumar, B. Bhushan, P. Dubey, I. Matai, A. Sachdev and G. Packirisamy, *Int. Nano Lett.*, 2013, 3, 45.
[72] A. Babu, A. K. Templeton, A. Munshi, R. Ramesh, *J. Nanomat.*, 2013, http://dx.doi.org/10.1155/2013/863951.
[73] S. Mukherjee, D. Chowdhury, R. Kotcherlakota, S. Patra, V. Kumar, M. P. Bhadra, Sreedhar, C. R. Patra, *Theranostics*, 2014, 4, 316.

[74] I. M.-Tynga, A. El-Hussein, M. A.-Harith, H. Abrahamse, *Int. J. Nanomed.*, 2014, 9, 3771.
[75] G. Zhou, W. Wang, *Orient J Chem.*, 2012, 28, 651.
[76] J. W. Han, S. Gurunathan, J.-K. Jeong, Y.-J. Choi, D.-N. Kwon, J.-K. Park, J.-H. Kim, *Nanoscale Res. Lett.*, 2014, 9, 1.
[77] R. Govender, A. Phulukdaree, R. M Gengan, K. Anand, A. A. Chuturgoon, *J. Nanobiotech.*, 2013, doi: http://www.jnanobiotechnology.com/content/11/1/5.
[78] M. Valodkar, R. N. Jadeja, M. C. Thounaojam, R. V. Devkar, S. Thakore, *Mat. Sci. Eng. C*, 2011, 31, 1723.
[79] B. Venkatesan, V. Subramanian, A. Tumala, E. Vellaichamy, *Asian Pac. J. Trop. Med.*, 2014, 7, S294.
[80] I. Sur, M. Altunbek, M. Kahraman, M. Culha, *Nanotechnol.*, 2012, 23, 375102.
[81] R. Foldbjerg, D. A. Dang, H. Autrup, *Arch Toxicol.*, 2011, 85, 743.
[82] R. R. Attia, L. A. Gardner, E. Mahrous, D. J. Taxman, L. Legros, S. Rowe, *J. Biol. Chem.*, 2008, 283, 30788.
[83] L. Cunningham, R. Aplenc, *Expert Opin. Pharmacother*, 2007, 8, 2519.
[84] C. H. Pui, S. Jeha, *Nat. Rev. Drug Discov.*, 2007, 6, 149.
[85] R. Basha, N. Sabnis, K. Heym, W. P. Bowman, A. G. Lacko, *Front. Oncol.* 2014, doi: 10.3389/fonc.2014.00101.
[86] D. Guo, Y. Zhao, Y. Zhang, Q. Wang, Z. Huang, Q. Ding, Z. Guo, X. Zhou, L. Zhu,
[87] N. Gu, *J. Biomed.Tech.*, 2014, 10, 669.
[88] R. Sankar, A. Karthika, A. Prabua, S. Karthik, K. S. Shivashangari, V. Ravikumar, *Colloids Surf. B: Biointerfaces*, 2013, 108, 80.
[89] D. Guo, J. Zhang, Z. Huang, S. Jiang, N. Gu, *Colloids Surf. B: Biointerfaces*, 2015, 126, 198.
[90] G. M. Sulaiman, E, H. Ali, I. I. Jabbar, A. H. Saleem, *Dig. J. Nanom. Biostruct.*, 2014, 9, 787.
[91] R. Thombre, S. Mehta, J. Mohite, P. Jaisinghani, *Int. J. Pharma Bio Sc.*, 2013, 4, 184.
[92] D. Bonnet, J. E. Dick, *Nature Med.*, 1997, 3, 730.
[93] D. Guo, L. Zhu, Z. Huang, H. Zhou, Y. Ge, We. Ma, J. Wu, X. Zhang, X. Zhou, Y. Zhang, Y. Zha, N. Gu, *Biomater.*, 2013, 34, 7884.
[94] A. Avalosa, A. I. Hazaa, D. Mateoa, P. Morales, *J. Appl. Toxicol.*, 2014, 34, 413.
[95] F. M.-Gutierrez, P. L. Olive, A. Banuelos, E. Orrantia, N. Nino, E. M. Sanchez, F.
[96] Ruiz, H. Bach, Y. Av-Gay, *Nanomedicine*, 2010, 6, 681.
[97] D. Shangguan, L. Meng, Z. C. Cao, Z. Xiao, X. Fang, Y. Li, D.Cardona, R.P. Witek,
[98] Liu, W. Tan, *Anal. Chem.*, 2008, 80, 721.
[99] S. A. Loutfy, R. H. Shalaby, A. R. Hamed, M. B. Mohamed, A. Barakat, Z. F.
[100] Abdullah, H. Yousef, A. Tamim, H. E. Eldin, N. M. Hegazy, *J. Chem. Pharma. Res.*, 2015, 7, 470.
[101] F. S. Rosarin, V. Arulmozhi, S. Nagarajan, S. Mirunalini, *Asian Pac. J. Trop. Biomed.*, 2012, 1.
[102] B. K. Gaiser, S. Hirn, A. Kermanizadeh, N. Kanase, K. Fytianos, A. Wenk, N. Haberl, A. Brunelli, W. G. Kreyling, V. Stone, *Toxicol. Sci.*, 2013, 131, 537.
[103] W. Chunyan, S. Valiyaveettil, *RSC Adv.*, 2013, 3, 14329.
[104] J. A. J. Paul, B. K. Selvi, N. Karmegam, *Appl. Nanosci.*, 2015, 5, 937.
[105] E. C. Dreaden, M. A. Mackey, X. Huang, M. A. El-Sayed, *Chem.Soc. Rev.*, 2011, 40, 3391.
[106] L. A. Austin, B. Kang, C.-W. Yen, M. A. El-Sayed, *J. Am. Chem. Soc.*, 2011, 133, 17594.
[107] S. R. Satapathy, S. Siddharth, D. Das, A. Nayak, C. N. Kundu, *Mol. Pharma.*, 2015, 12, A. 4011.
[108] A. T. Phong, H. Dianna; O'Connor, J. Andrea, *Adv. Sci. Technol.*, 2014, 96, 9.
[109] M. Szymanski, R. Porter, G. V. Dep, Y. Wang, B. G. D. Haggett, *Phy. Chem. Chem. A. Phy.*, 2013, 13, 5383.
[110] S. Taheri, A. Cavallaro, S. N. Christo, P. Majewski, M. Barton, J. D. Hayball, K. A. Vasilev, *ACS Biomat. Sci. Eng.*, 2015, 1, 1278.
[111] M. Chen, Q. Yu, H. Sun, *Int. J. Mol. Sci.*, 2013, 14, 18488.
[112] D. Matthew Eby, H. R. Luckarift, G. R. Johnson, *Appl. Mat. Interfaces*, 2009, 1, 1553.
[113] M. A. Ansari, H. M. Khan, A. A. Khan, S. S. Cameotra, M. A. Alzohairy, *Indian J. Med. Microbiol.*, 2015, 33, 101.
[114] P. A. Tran, D. M. Hocking, A. J. O'Connor, *Mat. Sci. Eng.: C*, 2015, 47, 63.
[115] O.Lyutakov, I. Goncharova, S.Rimpelova, K.Kolarova, J.Svanda, V.Svorcik, *Mat. Sci. Eng.:C*, 2015, 49, 534.
[116] C. Li, B. Cai, J. Jin, J. Liu, X. Xu, J. Yin, L. Yin, *J. Mat. Chem. B*, 2015, 3, 8410.
[117] F. Furno1, K. S. Morley, B. Wong, B. L. Sharp, P. L. Arnold, S. M. Howdle, R.

[118] Bayston, P. D. Brown, P. D. Winship, H. J. Reid, *J. Antimicrob. Chem.*, 2004, 54, 1019.
[119] H. Matthias, H. Christian, *Nanobiomaterials in Clinical Dentistry*, 2013, 167.
[120] R. G.-Contreras, L. A.-Figueroa, C. M.-Rubalcava, R. J.- Martínez, S. C.-Guajardo, P. S. Reyna and H. Mendieta-Zeron., *Int. Dental J.*, 2011, 61, 297.
[121] I. M. Hamouda, *J. Biomed. Res.*, 2012, 26, 143.
[122] L. F. E.-Cristóbal, G. A. M.-Castañón, E. J. T.-Déctor, N. N.-Martínez, N. V. Z.- Alonso, J. P. L. Rodrigguez, *Mat. Sci.Eng.: C*, 2013, 2197.
[123] H. H. K. Xu, L. Cheng, K. Zhang, M. A. S. Melo, M. D. Weir, J M. Antonucci, N. J. Lin, S. L. Gibson, L. C. Chow, X. Zhou, *Nanobiomaterials Clinical Dentistry*, 2013, 109.
[124] S. Mary, A. S. Melo, L. Cheng, K. Zhang, M. D. Weir, L. K. A. Rodrigues, H. H. K. Xu, *Dental Mat.*, 2013, 29, 199.
[125] A. P. R. Magalhaes, L. B. Santos, L. G. Lopes, C. R. A. Estrela, C. Estrela, E. M. Torres, A. F, Bakuzis, P. C. Cardoso, M. S. Carriao, *ISRN Nanotech.*, 2012, doi:10.5402/2012/365438.
[126] I. D. Sideridou, M. M. Karabela, *Dental Materials*, 2009, 25, 1315.
[127] Fengwei Liu, Ruili Wang, Yuyuan Shia, Xiaoze Jiang, Bin Sun, Meifang Zhu, *Progress in Natural Science: Materials International*, 2013, 23, 573.
[128] A. Miresmaeili, M. Atai, K.Mansouri, N.Farhadian, *Iran. J. Orthodontics*, 2012, 7, 14.
[129] K. Zhang, M. Anne, S. Melo, L. Cheng, M. D. Weir, Y. Bai, H. H. K. Xu, *Dental Mat.*, 2012, 28, 842.
[130] M. M. Stevanovic, S. D. Skapin, I. Bracko, M. Milenkovic, J. Petkovic, M. Filipic, *Polymer*, 2012, 53, 2818.
[131] S. M. Arde, P. R. Salokhe, A. H. Mane, R. S. Salunkhe, *Chem Sci Rev Lett*, 2014, 3(11), 557.
[132] L. Rizzello, P. P. Pompa, *Chem. Soc. Rev.*, 2014, 43, 1501.
[133] C. M.-Jones, E. M. V. Hoek, *J. Nanopart. Res.*, 2010, 12, 1531.
[134] S. Mohanty, S. Mishra, P. Jena, B. Jacob, B. Sarkar, A. Sonawane, *Nanomedicine*, 2012, 8, 916.
[135] A. K. Prusty, P. Parida, *SAJP*, 2014, 3, 504.
[136] W. Salema, D. R. Leitnera, F. G. Zingla, G. Schratterc ,R. Prasslc, W. Goesslerd, J. Reidla, S. Schild, *Int. J. Med. Microbiol.*, 2015, 305, 85.
[137] S. Rajakannu, S. Shankar, S. Perumal, S. Subramanian, G. P. Dhakshinamoorthy, *Int. J. Current Microbio. Appl. Sci.*, 2015, 4, 944.
[138] H. Padalia, P. Moteriya, S. Chanda, *Arab. J. Chem.*, 2014, http://dx.doi.org/10.1016/j.arabjc.2014.11.015.
[139] A. Pasha, S. Baker, D. Rakshith, S. Satish, *Saudi Pharm. J.*, 2015, http://dx.doi.org/10.1016/j.jsps.2015.01.008.
[140] P. Velmurugan, M. Cho, S.-S. Lim, S.-K. Seo, H. Myung, K.-S. Ban, S. Sivakumar, K.-M. Cho, B.-T. Oh, *Mater. Lett.*, 2015, 138, 272.
[141] E. E. Khoury, M. Abiad, Z. G. Kassaify, D. Patra, *Colloids and surfaces B: Biointerfaces*, 2015, http://dx.doi.org/doi:10.1016/j.colsurfb.2015.01.050.
[142] D. Li, Z. Liu, Y. Yuan, Y. Liu, F. Niu, *Process Biochem.*, 2015, 50, 357.
[143] P. Logeswari, S. Silambarasan, J. Abraham, *J. Saudi Chem. Soc.*, 2012, http://dx.doi.org/10.1016/j.jscs.2012.04.007.
[144] S. Agnihotri, S. Mukherji, Suparna Mukherji, *RSC Adv.*, 2014, 4, 3974.
[145] V. S. Cardoso, P. V Quelemes, A. Amorin, F. L. Primo, G. G. Gobo, A. C. Tedesco, C. Mafud, Y. P. Mascarenhas, J. R. Corrêa, S. A. S. Kuckelhaus, C. Eiras, J. R. S.
[146] Leite, D. Silva, J. R. S. Júnior, *J. Nanotechnol.*, 2014, http://www.jnanobiotechnology.com/content/12/1/36.
[147] M. Singh, S. Singh, S. Prasad, I. S. Gambhir, *Dig. J. Nanomat. Biostruct.*, 2008, 3, 115.
[148] T. Mohasseli, S. Pourseyedi, *Inte. Res. J. Appl. Basic Sci.*, 2013, 6, 587.
[149] N. Aziz, M. Faraz, R. Pandey, M. Shakir, T. Fatma, A. Varma, I. Barman, R. Prasad, *Langmuir*, 2015, 31, 11605.
[150] S. kannaiyan, E. V. Andal, *Int. J. ChemTech Res.*, 2015, 8, 54.
[151] D. Kalpana, J. H. Han, W. S. Park, S. M. Lee, R. Wahab, Y. S. Lee, *Arab. J. Chem.*, http://dx.doi.org/10.1016/j.arabjc.2014.08.016, 2014.
[152] M. M. H. Khalil, E. H. Ismail, K. Z. El-Baghdady, D. Mohamed, *Arab. J. Chem.*, 2014, 7, 1131.

[153] J. Jena, N. Pradhan, B. P. Dash, P. K. Panda, B. K. Mishra, *J. Saudi Chem. Soc.*, 2014, http://dx.doi.org/10.1016/j.jscs.2014.06.005.
[154] [149] J. P. Shastri, M. G. Rupani, R. L. Jain, *J. The Textile Institute*, 2012, 103, 1234.
[155] K. Gopinath, S. Gowri, A. Arumugam, *J. Nanostructure Chem.*, 2013, http://www.jnanochem.com/content//2013.
[156] S. Agnihotri, S. Mukherji, S. Mukherji, *Nanoscale*, 2013, 5, 7328.
[157] D. Xiang, Y. Zheng, W. Duan, X. Li, J. Yin, S. Shigdar, M. L. O'Connor, M. Marappan, X. Zhao, Y.Miao, B. Xiang, C. Zheng, *Int. J. Nanomed.*, 2013, 8, 4103.
[158] F. Shao *J. Mater. Envi. Sci.*, 2014, 5, 587.
[159] J. C. Trefry, D. P. Wooley, *J. Virol. Met.*, 2013, 183, 19.
[160] L. Lu, R. W. Sun, R. Chen, C. K. Hui, C. M. Ho, J .M. Luk, G. K. Lau, C. M. Che, *Antivir. Ther.*, 2008, 13, 253.
[161] D. B.-Pinto, S. Shukla, N. Perkas, A. Gedanken, R. Sarid, *Bioconjugate Chem.*, 2009, 20, 1497.
[162] L. Sun, A. K. Singh, K. Vig, S. R. Pillai, S. R. Singh, *J. Biomed. Nanotech.*, 2008, 4, 149.
[163] J. V. Rogers, C. V. Parkinson, Y. W. Choi, J .L. Speshock, S. M. Hussain, *Nanoscale Res. Let.*, 2008, 8, 129.
[164] P. Mehrbod, N. Motamed, M. Tabatabaian, E. R. Soleimani, E. Amini, M. Shahidi, M. T. Kheiri, *DARU J. Pharm. Sci.*, 2009, 17, 88.
[165] D. X. Xiang, Q. Chen, L. Pang, C. L. Zheng, *Journal of Virol. Met.*, 2011, 178, 137.
[166] J. L. Elechiguerra, J. L Burt, J. R Morones, A. C.- Bragado, X. Gao, H. H Lara, M. J. Yacaman, *J. Nanobiotech.* 2005, doi:10.1186/1477-3155-3-6.
[167] R. A. Frazer, *J. Nanomed. Nanotech.*, 2012, http://dx.doi.org/10.4172/2157- 7439.1000127.
[168] H. H Lara, N. V A.-Nuñez, L. I.-Turrent, C. R.-Padilla, *J. Nanobiotech.*, 2010, http://www.jnanobiotechnology.com/content/8/1/1.
[169] Y. Li, M. Hong, B. Qiu, Z. Lin, Z. Cai, Y. Chen, G. Chen, *Chem. Comm.*, 2013, 49, 10563.
[170] B. Schwarz, N. Schweizer, F. Po¨rll, G. Proll, G. Gauglitz, *Procedia Engineering*, 2010, 5, 906
[171] D. X. Xiang, Q. Chen, L. Pang, C. L. Zheng, *J. Virol. Met.*, 2011, 178, 137.
[172] Y. Mori1, T. Ono, Y. Miyahira, V. Q. Nguyen, T. Matsui, M. Ishihara, *Nanoscale Res. Lett.*, 2013, http://www.nanoscalereslett.com/content/8/1/93.
[173] M. Fatima, N. S. Zaidi, D. Amraiz, F. Afzal, *J. Micribiol. Biotech.*, 2015, doi: 10.4014/jmb.1508.08024.
[174] S. Gaikwad, A. Ingle, A. Gade, M. Rai, A. Falanga, N. Incoronato, L. Russo, S. Galdiero, M. Galdiero, *Int. J. Nanomed.*,2013, 8, 4303.
[175] R. L. Hu, S. R. Li, F. J. Kong, R. J. Hou, X. L. Guan and F. Guo, *Genetics Mol. Res.*, 2014, 13(3), 7022.
[176] P. Orlowski, E. Tomaszewska, M. Gniadek, P. Baska, J. Nowakowska, J. Sokolowska, Z. Nowak, M. Donten, G. Celichowski, J. Grobelny, M. Krzyzowska, *Plos one*, 2014, doi:10.1371/journal.pone.0104113.

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