A review on green synthesis of biocidal silver nanoparticles (Ag-NP) and it's anticancerous applications.

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Abstract

With the development of the biogenic nanotechnologies, scientists are looking new ways to design novel strategies for the treatment and diagnosis of cancer. Advances in nanotechnology have attracted many researchers to the biogenic synthesis of metallic NPs because of its advantages like, simple, fast, economical and biocompatibility. Many plants with medicinal value have been selected as reservoirs of diverse phytochemicals for the biogenic synthesis of silver nanoparticles (Ag-NPs).In this review, the top point discussed is mechanistic advances in the synthesis of Ag-NPs from bacteria & fungi to plant extract and the recent improvements achieved in the use of biogenic Ag-NPs as cancer therapeutic agents in hope that biogenic Ag-NPs may become a potential cancer therapeutic and diagnostic agent in the near future.

Introduction

Use of silver and gold is as old as human civilization but the nanoparticles (NPs) has only recently been recognized. They have been specifically used in agriculture and medicine as antibacterial, antifungal and antioxidants. It has been demonstrated that Ag-NPs arrest the growth of bacteria by binding Ag/Ag+ with the biomolecules present in the microbial cells or produce reactive oxygen species and free radicals which cause apoptosis leading to cell death preventing their replication. Since Ag-NPs are smaller than the microorganisms, they diffuse into cell and rupture the cell wall as observed in SEM and TEM images of the suspension containing nanoparticles and pathogens. The toxicity of Ag-NPs is dependent on the size, concentration, pH of the medium and exposure time to pathogens. In the last decade, numerous efforts were made to develop green methods of synthesis to avoid the hazardous byproducts. This review describes the methods of green synthesis for Ag-NPs and their numerous applications. The formation of Ag-NPs has received significant interest because of their potential application in antimicrobial activities (Savithrama et al.2011; Rao et al. 2009), DNA sequencing (Cao et al. 2001), climate change and contamination control (Shan et al.2009),

clean water technology (Savage and Diallo 2005) and biomedical applications (Hullmann 2007).

Biosynthesis of NPs by means of green rout does not use toxic chemicals, therefore, the development of green synthesis of Ag-NPs is advancing as a key branch of nanotechnology where the use of biological entities like plant, plant extract or microorganisms biomass are used as alternative to chemical and physical methods in an ecofriendly method for the generation of NPs alternative Reddy et al.2012).

High-temperature, energy, pressure, and harmful chemicals are not required for green synthesis (Ahmed et al. 2016b) Hence, this review describes the green-inspired synthesis of Ag-NPs that can provide advantage over the physical and chemical methods. Green synthesis does not involve the use of any toxic chemicals, it is cost-effective, environment friendly, zero energy based and less time consuming process. Moreover it does not require the use of any kind of stabilizers. Various environmental friendly materials like plant extracts, bacteria, actinomycetes, fungi and enzymes are categorized and used as sources under "green synthesis". SNPs synthesized by green process are highly compatible for pharmaceutical and other biomedical applications (A.K. Mittal, et al 2013). Various plant resources have been explored by researchers till date to synthesize silver nanoparticles (k.P. Bankura et al 2012) (Y.S. Rao et al 2013) (N.M.shinde et al 2014) (V.kathiravan 2014) (P.U. Rani 2014) The key phytochemicals responsible for converting silver ions into silver nanoparticles are found to be terpenoids, glycosides, alkaloids, phenolics (flavonoids, coumarins, ubiquinones, tannins, etc.) as identified in IR spectroscopic studies (R. Mariselvam and C krishraj et al. 2014 & 2010) One of the commonest plant products used for daily consumption is the seed (bean) of Coffea arabica fam. Rubiaceae. The bean of this plant was earlier reported to contain good levels of phenolic compounds and thus, it could be used as a potential bioreductant to produce SNPs.

Synthesis of Ag-NPs by using bacteria

Ag-NPs are known to be bactericidal but some bacteria are known to be Ag resistant (Slawson et al. 1992).Therefore, these bacteria can aggregate Ag on the cell walls, hence recommending their utilization in industrial recovery of Ag from ore materials (Pooley 1982). Initially, Klaus et al.(1999) reported that, Ag-NPs were synthesized by using Ag resistant bacterial strains Pseudomonas stutzeri AG259 that was isolated from silver mine. These cells accumulate Ag-NPs in large amounts . This microorganism can survive metal ion concentrations and due to it's resistance to the metal. The mechanisms involved in the resistance are efflux systems, alteration of solubility and toxicity via reduction or oxidation, biosorption, bioaccumulation, extracellular complex formation or precipitation of metals. There is also another aspect that though these organisms can grow at lower concentrations, their exposure to higher

concentrations of metal ions can induce toxicity. The most widely accepted mechanism of silver biosynthesis by bacteria is the presence of the nitrate reductase enzyme which converts nitrate into nitrite.The size of the Ag- NPs synthesized by these bacteria observed by Klaus et al (1999) with Transmission Electron Microscope (TEM) was 200 nm. Shivaji et al. (2011) synthesized Ag-NP using culture supernatants of cryophilic bacteria. Kalimuthu et al. (2008) illustrated the synthesis of Ag-NPs by Bacillus licheniformis, where the aqueous solution of AgNO3 added to the biomass of B. licheniformis, the color change from whitish-yellow to brown(observed by UV spectrometer) indicates the formation of Ag-NPs with the size range of 50nm. Ag-NPs were also synthesized by Nanda and Saravanan (2009) using culture supernatants of Staphylococcus aureus, *Escherichia coli* (El-Shanshoury, 2011), *Actinobacteria rhodococcus* sp. (Otari, 2012), *Pseudomonas* sp. (Thomas *et al*., 2012). Besides the advantages, it is necessary to ensure that bacteria kept on growing after the formation of Ag-NPs. Except this, the main disadvantage of utilizing bacteria as nanofactories is the slow synthesis rate and the limited number of sizes and shapes obtained as compare to conventional methods. Therefore, fungi based nanofactories and chemical reduction reaction including plant and plant extracts based materials were investigated for Ag-NPs synthesis (Kharissova et al.2013).

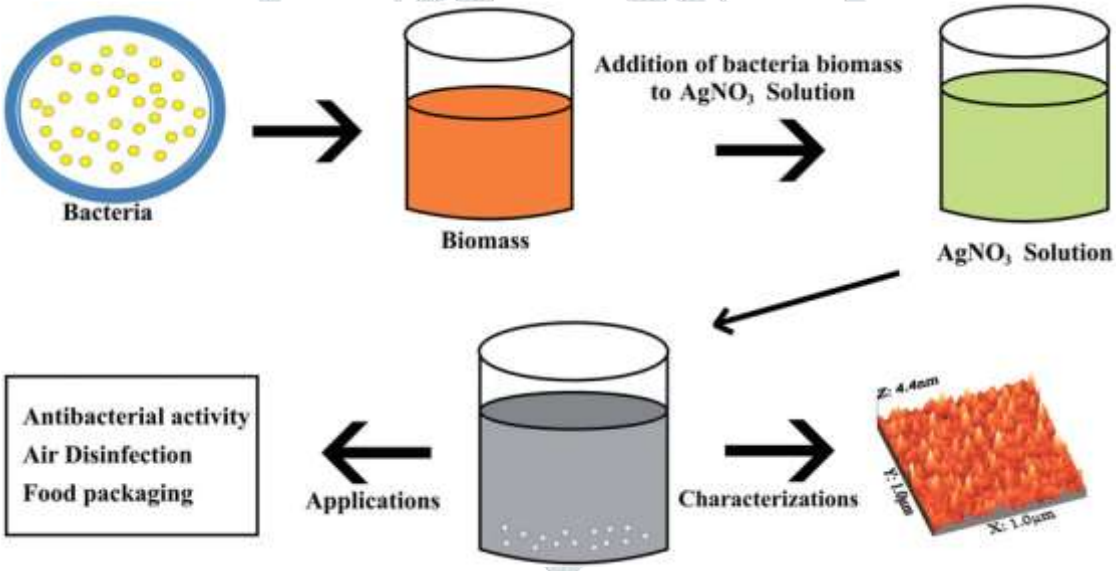

Fig- Biosynthesis of Ag-NP by bacteria

Synthesis of Ag-NPs by using fungi

Fungi have potential for the synthesis of metallic NPs due to their metal accumulation capacity,high tolerance and intracellular uptake like bacteria. Fungi are easy to handle in a research facility as compare to bacteria (Sastry et al. 2003). When in comparison with bacteria, fungi can produce larger amounts of nanoparticles because they can secrete larger amounts of proteins which directly translate to higher productivity of nanoparticles. The silver nanoparticle production by fungi is said to follow the following steps - trapping of Ag+ ions at the surface of the fungal cells and the subsequent reduction of the silver ions by the enzymes

present in the fungal system.The extracellular enzymes like naphthoquinones and anthraquinones are said to facilitate the reduction. Considering the example of F. oxysporum, it is believed that the NADPH-dependent nitrate reductase and a shuttle quinine extracellular process are responsible for nanoparticle formation The extracellular synthesis of Ag-NPs by utilizing F. oxysporum and its antibacterial effect on textile fabrics is studied by Dur_an et al. (2007). Vigneshwaran et al.(2007) reported that mono-disperse Ag-NPs can be synthesized by using fungus Aspergillus flavus The extracellular synthesis of Ag-NPs in the range of 10-100nm using fungus Cladosporium cladosporioides is observed by Balaji et al. (2009)). In another method, Kathiresan et al. (2009) illustrated in vitro synthesis of Ag-NPs using AgNO3 as a substrate and Penicillium fellutanum isolated from coastal mangrove sediment. The extracellular synthesis of mono-dispersed Ag-NPs is achieved by Bhainsa and D'Souza (2006) using Aspergillus fumigatus at quick synthesis rate. Spherical Ag-NPs are synthesized by Li et al. (2011) using Aspergillus terreus with an average size of 1–20 nm.In fungi-based synthesis, NPs are formed on the surface of mycelia, not in solution. In first step, Ag particles were adsorbed on the surface of the fungal cells due to the presence of electrostatic interaction between negatively charged carboxylate groups in enzymes and positively charged Ag ions. The Ag particles are reduced by the enzymes present in cell walls, prompting the development of Ag nuclei. The Ag-NPs were also synthesized by Vahabi et al. (2011) using fungus Trichoderma reesei in the size range of 5–50 nm.

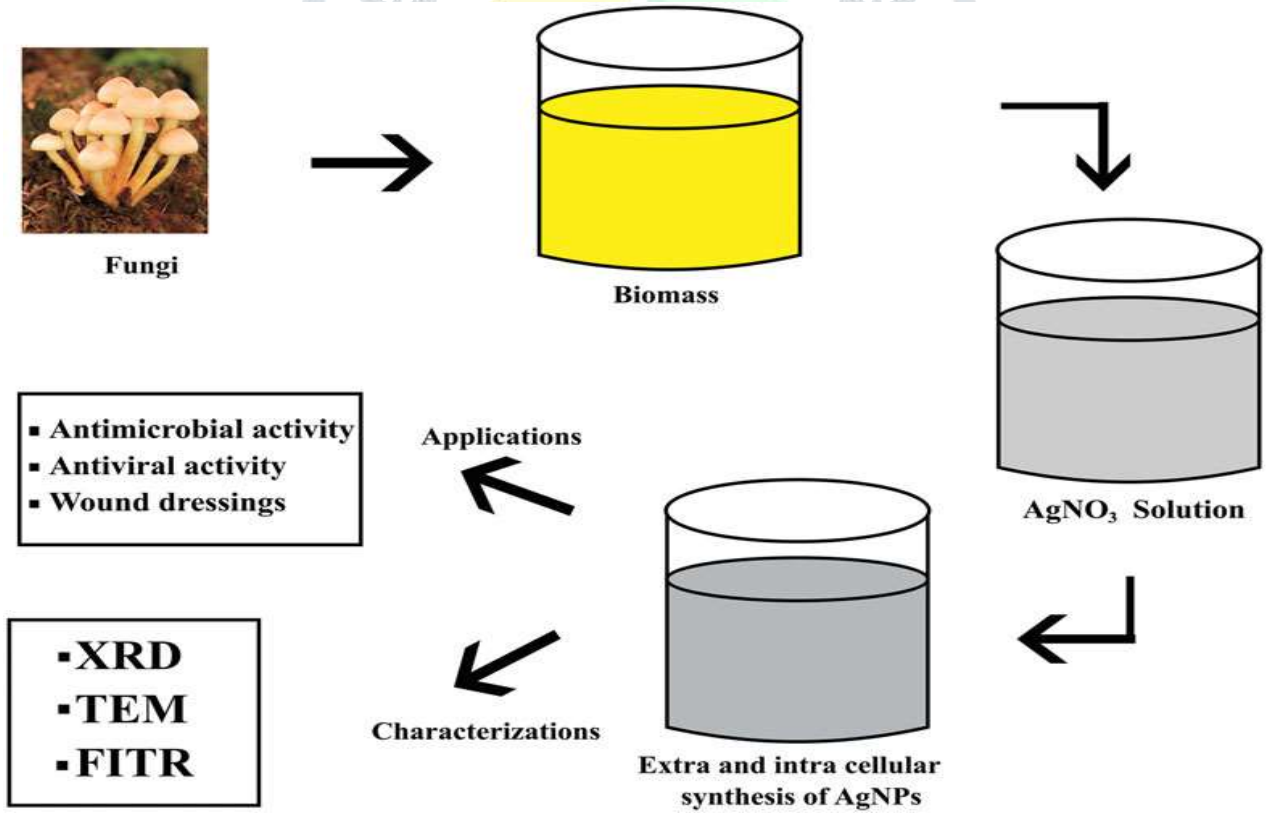

Fig – Synthesis of silver nano particles by fungi

Synthesis of Ag-NPs by using plant and plant extracts

The use of plant and plant extracts in green synthesis has drawn attention because of its rapid growth, providing single step technique, economical protocol, non-pathogenic, and eco-friendly for NPs synthesis. The main phytochemicals involved are terpenoids, flavones, ketones, aldehydes, amides, and carboxylic acids. Flavones, organic acids, and quinones are water-soluble phytochemicals that are responsible for the immediate reduction of the ions. Studies have revealed that xerophytes contain emodin, an anthraquinone that undergoes tautomerization, leading to the formation of the silver nanoparticles. In the case of mesophytes, it was found that they contain three types of benzoquinones: cyperoquinone, dietchequinone, and remirin. It was suggested that the phytochemicals are involved directly in the reduction of the ions and formation of silver nanoparticles The schematic diagram for the green synthesis of Ag-NPs using plant or plant extract is shown in Figure.

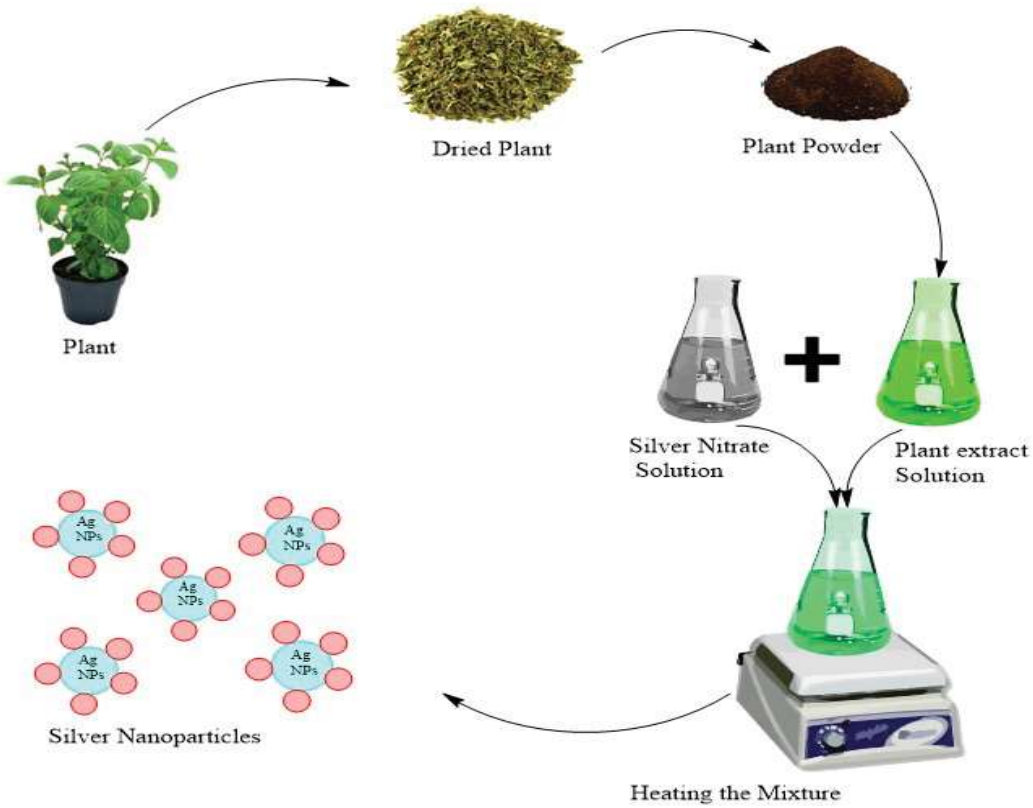

Fig – Green synthesis of silver nano-particles (Ag-NP) using plant extract

Gardea-Torresdey et al. (2003) illustrated that the first approach of using plants for the synthesis of metallic NPs was done by using Alfalfa sprouts, which was the first description about the synthesis of Ag-NPs using living plant system. Alfalfa roots have the ability to absorb Ag from agar medium and transport them into shoots of plant in same oxidation state. In shoots, these Ag atoms arranged themselves to produce Ag-NPs. Ahmad and Sharma (2012) reported that Ag-NPs are synthesized by utilizing Ananas comosus (pineapple juice) as stabilizing as well as reducing agent and synthesized NPs were characterized by High

Resolution Transmission Electron Microscopy (HRTEM), UV–Vis spectrometer, Energy Dispersive X-ray Spectroscopy (EDX), and Selected Area Diffraction (SAD). TEM micro-graphs represented the spherical NPs with an average diameter of 12 nm. Ag-NPs are synthesized with same technique and their characterization method by using different plants and plant extracts. Singh et al.(2010) synthesized Ag-NP of 30nm size utilizing Argemone mexicana leaf extract as capping as well as reducing agent by adding to the aqueous solution of AgNO3. Gavhane et al. (2012) studied that Ag-NPs 0f 43 to 59 nm size were synthesized by the reduction of aqueous AgNO3 solution through the extract of Neem and Triphala. Velmurugan et al. (2015) illustrated that Ag-NPs are synthesized by peanut shell extract and their characteristics and antifungal activity is compared with commercial Ag-NPs. spherical Ag-NPs with an average diameter of 20nm were also synthesized by Roy et al. (2014)using the fruit extract of Malus domestica as capping agent. Kaviya et al. (2011) synthesized Ag-NPs by using Polyalthia longifolia leaf extract as reducing agent along with D-sorbital to enhance the stability of NPs.

Ag-NPs were synthesized by Maqdoom et al. (2013) using the fruit extract of Papaya and are characterized by Absorption spectroscopy and FTIR. Rout et al. (2012) reported that spherical-shaped Ag-NPs were synthesized by using Ocimum sanctum leaf extract as stabilizing agent. Awwad et al. (2013) studied that spherical Ag-NPs were also synthesized by using carbo leaf extract with an average particle size from 5 to 40 nm. Bar et al. (2009) represented that Ag-NPs were synthesized by reduction of aqueous AgNO3 solution using latex of Jatropha curcas as capping agent. Udayasoorian et al. (2011) illustrated that Ag-NPs were also synthesized by using the leaf extract of Cassia auriculata as reducing as well as capping agent. Kasthuri et al. (2009) synthesized Ag-NPs of size range between21-39nm by reduction of aqueous Ag ions through leaf extract of Apiin as capping and reducing agent. Shankar et al. (2003) represented the extracellular synthesis of Ag-NPs of size 40nm by Geranium leaf extract. Stable and spherical

Ag-NPs were synthesized by Saware et al. (2014) by using Ficus benghalensis leaf extract with an average particle size 10–50 nm. Nakkala et al. (2014) studied that Acorus calamus extract can be used as capping agent for the synthesis of Ag-NPs and evaluate it's anticancer, and antibacterial effect. Kumar et al. (2014) reported that Ag-NPs are synthesized using the extracts of Boerhaavia diffusa, XRD and TEM results showed an average size 25nm having face-centered cubic geometry with spherical shape. These NPs were used for antibacterial action against three fish bacteria, namely Pseudomonas fluorescens, Aeromonas hydrophila, and Flavobacterium. Krishnaraj et al. (2010) synthesized Ag-NPs by using the leaf extract of Acalypha indica. Dwivedi and Gopal(2010) reported that spherical Ag-NPs are synthesized by using obnoxious weed Chenopodium album with size range 10–30nm as measured by TEM. In another method, synthesis of Ag-NPs is reported by Aldebasi et al. (2015) using an aqueous mixture of Ficus carica leaf extract. Ag-NPs are synthesized by Awwad et al. (2012) using the

extract of Olea europaea and characterized by using SEM, XRD, and FTIR. The spherical Ag-NPs have been synthesized using the extract of Abutilon indicum and also studied their high antimicrobial activity against S. typhi, E. coli, S. aureus, and B. subtilis microorganism by Ashokkumar et al. (2015).Awwad and Salem (2012) reported that mono-dispersed and spherical Ag-NPs were synthesized by using Mulberry leaves extract with average particle size of 20 nm. The characteristics of synthesized Ag-NPs were analyzed by UV–Vis spectroscopy, XRD and SEM as well as revealed their effective antibacterial activity towards Staphylococcus aureus and Shigella sp. Khalil et al. (2014) studied that Ag-NPs are synthesized by the reduction of AgNO3 solution through olive leaf extract and these particles showed effective antibacterial activity against drug-resistant bacteria isolates.

Alternanthera dentate leaf extract was used as a capping agent for green synthesis of Ag-NPs by Kumar et al. (2014). Bindhu and Umadevi 2013). Muruganet al. (2014) reported that Ag-NPs are synthesized by using Acacia leucophloea extract in size range upto 38–72 nm. Arokiyaraj et al. (2014) reported that, Ag-NPs were synthesized using Chrysanthemum indicum. L. and NPs within the size range 17–29 nm. Kumar et al. (Ashok 2012; Kumar et al.2013) have shown that, Ag-NPs were synthesized by using the leaf extract of Parthenium hysterophorus, Premna herbacea. Recently, Rodr_ıguez-Le_on et al. (2013) reported that Ag-NPs are also synthesized using the Rumex hymenosepalus extract Thus, the use of plant extract in green synthesis has stimulated various investigations and studied till now. It was demonstrated that the formation of metal NPs using plant extract could be finished in the metal salt solution within short duration at room temperature depending upon the nature of plant extract. After the selection of the plant extract, the main affecting parameters are the concentration of the extract, temperature, metal salt, pH, and contact time (Mittal et al. 2013). The benefits of using plants for the formation of NPs are that plants are easily accessible and safe to handle and have a large range of active agents that can advance the reduction of Ag ion. Mainly the plant parts like roots, latex,stem, seeds, and leaves are being used for NPs synthesis(Kharissova et al. 2013). The interesting point is the active agent presents in these parts, act both as reducing and stabilizing agent that produce stable and shape-controlled NPs. Main compounds which influence the reduction and capping of the NPs are biomolecules, i.e., terpenoids, polysaccharides, phenolics, alkaloids, flavones, amino acids, alcoholic compounds, enzymes, and proteins. Similarly, chlorophyll pigments and quinal, methyl chavicol, linalool, caffeine, eugenol, ascorbic acid, theophylline, and other vitamins have also been investigated (Sharma et al. 2009;

Need For Green syntesisis & why nanosilver?

Biosynthesis of nanoparticles is a kind of bottom up approach where the main reaction occurring is reduction/oxidation. The need for biosynthesis of nanoparticles rose as the physical and chemical processes were costly and included toxic chemicals that may have adverse effect in the medical applications (parasharu et al 2009). This is not an issue when it comes to biosynthesized nanoparticles via green synthesis route (bagun et all 2009)]. So, in the search of cheaper and biocompatible pathways for nanoparticles synthesis, scientist used microbial enzymes and plant extracts (phytochemicals). The phytochemicals being released in the body might not have a good efficacy towards the targeting of the microbes and cancer cells due to its low diffusion characteristics and failure of overcoming the anatomical barriers (M. Ramaya et al 2012). Since the structure and nanosize of the silver particle makes it successful in easy diffusion and overcoming the barriers so Ag-NP are used.,Soluble silver compounds such as silver salts, have been used in treating mental illness, epilepsy, gastroenteritis and infectious diseases including syphilis and gonorrhea (J.D. et al 2005). Metallic silver appears to pose minimal risk to health, whereas soluble silver compounds are more readily absorbed and have the potential to produce adverse effects (J. D. et al 2005)]. Since silver in any form is not thought to be toxic to the immune , cardiovascular, nervous or reproductive system and it is not considered to be carcinogenic . therefore silver is relatively non-toxic (Chen. X. et al 2008)

Action of silver nanoparticles on microbes:

The exact mechanism which silver nanoparticles employ to cause antimicrobial effect is not clearly known and is a debated topic. There are however various theories on the action of silver nanoparticles on microbes to cause the microbicidal effect. Silver nanoparticles have the ability to anchor to the bacterial cell wall and subsequently penetrate it, thereby causing structural changes in the cell membrane like the permeability of the cell membrane and death of the cell. There is formation of “pits” on the cell surface, and there is accumulation of the nanoparticles on the cell surface (sondi et al 2004)]. The formation of free radicals by the silver nanoparticles may be considered to be another mechanism by which the cells die. There have been electron spin resonance spectroscopy studies that suggested that there is formation of free radicals by the silver nanoparticles when in contact with the bacteria. These free radicals have the ability to damage the cell membrane and make it porous which can ultimately lead to cell death (Danilauk and Kim 2006/7). It has also been proposed that there can be release of silver ions by the nanoparticles (feng et al 2008), and these ions can interact with the thiol groups of many vital enzymes and inactivate them (Matsumura et al 2003). The bacterial cells in contact with silver take in silver ions, which inhibit several functions in the cell and damage the cells. Then, there is the generation of reactive oxygen species, which are produced possibly

through the inhibition of a respiratory enzyme by silver ions and attack the cell itself. Silver is a soft acid, and there is a natural tendency of an acid to react with a base, in this case, a soft acid to react with a soft base . The cells are majorly made up of sulfur and phosphorus which are soft bases. The action of these nanoparticles on the cell can cause the reaction to take place and subsequently lead to cell death. Another fact is that the DNA has sulfur and phosphorus as its major components; the nanoparticles can act on these soft bases and destroy the DNA which would definitely lead to cell death (Morones et al 2005]. The interaction of the silver nanoparticles with the sulfur and phosphorus of the DNA can lead to problems in the DNA replication of the bacteria and thus terminate the microbes growth. It has also been found that the nanoparticles can modulate the signal transduction in bacteria. It is a well established fact that phosphorylation of protein substrates in bacteria influences bacterial signal transduction. Dephosphorylation is noted only in the tyrosine residues of gram-negative bacteria. The phosphotyrosine profile of bacterial peptides is altered by the nanoparticles. It was found that the nanoparticles dephosphorylate the peptide substrates on tyrosine residues, which leads to signal transduction inhibition and thus the stoppage of growth. It is however necessary to understand that further research is required on the topic to thoroughly establish the claims .

Mechanisms of Antibacterial Effects of Ag NPs

1.Cell death due to uncoupling of oxidative phosphorylation
2.Cell death due to induction of free radical formation
3.Interference with respiratory chain at Cytochrome C level
4.Interference with components of microbial ETS
5.Interactions with protein thiol groups & membrane bound enzymes
6.Interaction with phosphorous- and sulfur-containing compounds such as DNA

Silver Nanoparticles as Anti-Cancer Agent

Green synthesized AgNPs are not only subjugated for the therapy of different types of cancers, but also have promising application in diagnosis, such as bio-sensing, bio-imaging and MRI imaging, among other applications. Inorganic nanoparticles significantly interact with cells and intracellular macromolecules like proteins and DNA. Cellular up-take of nanoparticles leads to era of reactive oxygen species which provoke oxidative stress. Moreover, nanoparticles easily cross the nuclear membrane and therefore they can interface with DNA specifically or indirectly although the exact mechanism for this interaction is not yet known [46]. It is clearly proven that synthesized AgNPs induces cell damage through the loss of cell membrane integrity, oxidative stress and apoptosis. AgNPs treated MCF-7 cells indicated most readily

clear effect is the alteration in cell shape apparent morphological variations for example, coiling and cell shrinkage compared to control cells. Bio-synthesized AgNPs cause cellular damage in Hep-2 cell line through the formation of ROS was reported (chaudhari et al 2016). The silver nanoparticle has the capacity of reducing the cell viability percentage of HeLa cell line as studied by (Sonia sarkar et al 2018) using pomegranate extractas reducing medium for AgNP synthesis. Khan Y et al 2017 demonstrated Bio-Synthesized Silver Nanoparticles Using Different Plant Extracts as Anti-Cancer Agent In the future, biogenic AgNPs will be promising entities subjugated for diagnosis of cancer due to their self-fluorescence ability. The emission of bright red fluoresce inside the cancerous cell upon treatment with biogenic AgNPs clearly indicates the internalization of these nanoparticles by cells. While incubating the cells with these nanoparticles it enters inside the cell having fluorescent molecules attached during synthesis (Wolfbeis OS 2015). AgNPs should be properly assessed for their potential toxicity, biocompatibility and side effects (Sportelli MC et al 2016) before testing on humans.

Effect of AgNPs on pro- and antiapoptotic gene expression

AgNPs, downregulated the expression of Bcl-2, but upregulated the expression of p53, p21, Bax, Bak, and caspase-9 and -3. p53 can inhibit cell growth via activation of cell cycle arrest and apoptosis. Our results suggest that AgNPs can upregulate the expression of p53 and p21. Hill et al 68 reports that Ag-NP strongly induces p53-dependent apoptosis, which correlates with the accumulation of proapoptotic proteins, such as PUMA and Bax, in human colon cancer cells. In A2780 cells, the upregulation of p53 is accompanied by increased expression of p2l, indicating that AgNPs sensitize the cells to apoptosis.

An experiment reported by Asharani et al. in 2009 about the treatment of cells with AgNPs explains calcium transients. The release of Ca+ from the intracellular stores can be inhibited by the high concentration of Ag+ released from AgNPs. Oxidative stress is linked with Ca2+ transient that ultimately increases permeability changes of mitochondria inducing apoptosis.

Mitochondria,Caspase3/9 Pathways and Apoptosis by the AgNPs

Pores in mitochondrial membrane are opened and then the membrane is disrupted during the apoptosis process. When cells are treated with AgNPs, they show a decrease in the red fluorescence while the green fluorescence is increased. The opening of mitochondrial membrane is controlled by two genes; one gene “Bcl-2” prevent its opening while the second gene “Bax” accelerate it (Bonra M 2015)].Apoptosis signal are induced by the AgNPs *via* a caspas dependent pathway along with the involvement of mitochondria. Caspase 9/3 can be activated by AgNPs by time dependent manner stimulated by the disruption of mitochondrial membrane. Previous studies suggest that the process of apoptosis is stimulated by AgNPs

through the presence of ROS in *in vitro* systems (Ahmed et al 201).Signal generated by mitochondria have an important role in apoptosis and many regulators of apoptosis can induce the inhibition of the integrity of mitochondria during the apoptosis process (Vyas S et al 2016).Usually the caspase pathway is activated due to the oxidative stress caused by the release of cytochrome c from the intermembrane space of the mitochondria into the cytosol (Almeida et al 20158).

bAgNPs Enhance Cytotoxicity of Chemotherapeutic Drug Cisplatin (CDDP).

Cisplatin, a widely used therapeutic drug is part of the treatment regime for cancer. However, almost 30 years after the introduction of CDDP into clinical settings, we are still in an effort to understand how to refine the therapeutic potential of cisplatin. Despite its proven benefits, CDDP-based treatment is often associated with life threatening toxicity limiting its clinical application(Babu et al 2015),this perpetually demands for identification of novel, biological molecules that can act as a complement to the potent drug CDDP. Keeping these facts in mind, Bau et al 2015 analyzed whether the protein-capped bAgNPs that showed cytotoxicity against cancer cells(OS and Huh7 cells) have prospective potential to increase CDDP induced cytotoxicity. their result shows that bAgNPs can efficiently increase the cytotoxic ability of the potent drug,CDDP. to investigate the effect of bAgNPs on the apoptotic pathway, the caspase-3 enzyme activity was examined in OS cells through an ELISA-based method.The enzyme activity increased in a dose-dependent manner in bAgNP-treated cells, An increase in the caspase activity was further confirmed by the detection of cleaved caspase-3, an indicator of apoptosis, by immunoblot.

Other Applications of Ag-NPs

Ag-NPs have numerous antimicrobial and antifungal applications. Ag-NPs have been broadly used as antibacterial coat in therapeutic applications, such as cardiovascular implants,wound dressings, catheters, orthopedic implants, dental composites, nano-biosensing, and agriculture engineering(He et al. 2016).

conclusion

biocompatibility of green synthesized AgNPs toward normal cells is beginning to a new era in the cancer diagnosis.Characterization and toxicity screening of biogenic AgNPs is strongly recommended before production at commercial scale. We hope that biogenic AgNPs might become a potential cancer nanomedicine in the near future. The rapid increase in demand of biogenic metal nanoparticles for multiple applications increases the need for their industrial production in stabilized formulations. Therefore, effort is being exerted on biological synthesis of AgNPs as cancer nanomedicine.For optimum yield, many parameters such as pH, temperature and incubation time, salt concentration need optimization.

The hidden phytochemical compounds of plants are responsible for reduction and stabilization of biogenic nanoparticles. Green synthesis of biogenic NPs for cancer diagnosis still needs a lot of research. Moreover, issues such as biocompatibility, bioavailability, toxicity

and clearance of AgNPs all need to be investigated in-depth *via in vivo* trails to develop potential therapeutic and diagnostic agents for cancer.

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