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ROLE OF GREEN SILVER NANOPARTICLES IN SUPPRESSING VARIOUS HUMAN PATHOGENESIS

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Abstract. The ability of microbial cells to use genetic modifications as a strategy for better survival and disseminate the changes with the community gives rise to the peril of antimicrobial resistance and multidrug resistance. Silver has long been known for its enhanced antimicrobial actions. Advancements in nanotechnology sciences has given a vent to the better applicability of silver salts, which is further enhanced by their green (plant mediated) synthesis resulting in Green Silver Nanoparticles (GSNPs). Apart from the antimicrobial actions, these particles have been found to be associated with the modulation of immune system and anticancer activities, bone cement additives, joint replacement therapies, dental fillings, wound dressings etc. The diagnostic domain of medical science applies these particles as an effective agent of biosensing. The established applications of silver nanoparticles in these areas strongly advocate the future researches related to the analysis of the role of phytochemicals in augmenting the activities of silver nanoparticles in case of green synthesis. This review focuses on surfacing the mechanisms of actions of GSNPs on human disease causing agents and conditions, which help may be helpful in developing the strategies for combating different pathological conditions in humans.

1. INTRODUCTION

The ever-expanding canopy of antimicrobial resistance and multidrug resistance to include more and more microorganisms has posed an imperative need in front of humanity to look for effective substitute to deal with the quandary as soon as possible. The emergence and spread of resistance among the microbial populace by means of genetic maneuvering against newly developed antibiotics in further endorse the necessity for innovation, diagnosis and prevention of human diseases [1]. Antibiotic resistance enhances the morbidity and mortality coupled with infections and plays a substantial role in the rising costs of care ensuing from extended hospital stays and the need for more expensive drugs. A number of pathogen-specific epidemiological models of drug resistance have been proposed for both community-acquired and hospital-acquired infections [2]. Most diseases that were previously characterized as being monomicrobial in nature are becoming increasingly recognized as true polymicrobial infections, involving the complex interaction of several microbial species. Different domains of antimicrobial science have merged together to combat the above predicament. Silver has long been identified for its effective antimicrobial properties. Ag^+ forms complexes with bases present in DNA and is a potential inhibitor of fungal DNAases [3-5], leading to enzyme inactivation by means of formatting silver complexes with electron donors containing oxygen, nitrogen, sulphur, thiols, phosphates, carbohydrates, hydroxyl, amines, imidazoles, indoles [4]. It causes dislocation of native metal cations from their usual binding sites in enzymes [5] and inhibit oxidation of glucose, glycerol, fumarate, and succinate in *E. coli* [4]. On the other hand the applicabil-

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ity and effectiveness of silver salts increase manifolds when used in nano size dimension due to a higher surface area to volume ratio. The nanosize of the particles also improves the penetration potential of the silver particles, hence aiding in better use of the metal properties [6]. Besides, these silver nanoparticles have a broad-spectrum effect, i.e. effective against a range of microorganism including bacteria and fungi, and are not yet linked with any major drug resistance. This is because an organism would have to undergo synchronized mutations in every crucial function within a single generation to escape its influence, which is common with antibiotics. Bacteria having a mutated genome sequence and resulting in antibiotic resistance pose a threat to human health. This is not only because they do not respond to conventional treatment methodologies but also due to the possibility of horizontal gene transfer to other bacteria. The bacteria mutate in such a way that the antibiotic is metabolized or eliminated out of the cell. Some of the specific target enzyme can also be mutated, that decreases the sensitivity of the bacteria for the antibiotic, which is not the case with silver based products. Besides, silver targets a number of cellular processes along with the membrane integrity, while antibiotics specifically target one process. Although in some cases resistance genes have been identified against silver which seem to be involved in pumping silver out of the cell [7,8]. Thus with the emergence of antibiotic-resistant bacteria, silver nanoparticles are re-emerging as modern medicine against which the pathogenic organisms have usually failed to develop an immunity [9].

The production of silver nanoparticles is mediated via two basic routes namely top down and bottom up methods. The top-down methods usually encompasses physical processes including mechanical grinding of bulk metal ions, freeze-drying, spread drying, precipitation and laser ablation. The methods introduce imperfections in the surface structure of the product which is a major limitation as the surface chemistry and other physical properties of nanoparticles are highly dependent on the surface structure [10-12]. Moreover the techniques involved in physical approach of silver nanoparticles synthesis like evaporation-condensation in furnaces and ceramic heaters have several drawbacks such as constraint of a large space for establishment, consumption of a great deal of energy thereby increasing the environmental temperature, obligation of prolonged time to achieve thermal stability, requirement of power consumption of more than several kilowatts and an extended preheating time to attain a stable operating temperature. On the other hand, the bottom-up approaches rely upon the chemical and biological reduction for the synthesis of silver nanoparticles. It requires a silver ions solution and a source of reducing agents such as borohydride, citrate, ascorbate, elemental hydrogen [13] and stabilizing agents such as polyvinyl alcohol and polyvinyl pyloridone. In the presence of the reducing agents, the silver ions (Ag^{+}) in aqueous solution generally formulate colloidal silver with particle diameters of several nanometers. Initially, the reduction of Ag^{+} ions with various complexes forms silver atoms (Ag^{0}), which is followed by agglomeration into oligomeric clusters [14]. These clusters ultimately lead to the fabrication of colloidal silver particles [15,16]. The stabilizing agents then prop into action and bind to the colloidal silver nanoparticles rendering them high stability by preventing their further agglomeration that may cause the assembly of larger sized particles beyond the nano (10^{-9}) range.

Of late a novel method of silver nanoparticles biosynthesis is swiftly gaining popularity in which the naturally occurring reducing and stabilizing agents obtained from bacteria, fungi, actinomycetes and plants extracts are employed to obtain silver nanoparticles (AgNPs). Such simple and viable substitute method of production in comparison to complex chemical synthetic procedures comes under the heading of green biosynthesis which is cost effective, environmental friendly, easy to scale up and avoids the involvement of harmful and toxic chemicals required in other chemical processes [17]. Among all the biological sources plants are the particularly important and viable options as the raw materials are abundantly available and there is the least obligations to maintain them in a pure culture form as in case of microorganisms. A variety of plant sources have been scrutinized for their ability to fabricate Green Silver Nanoaprticles (GSNPs) as summarized by Sinha and Manjhi, 2015 [12].

The GSNPs have been proved to have better antimicrobial properties [18] as compared to commercial antibacterial and antifungal products and can be used to combat various pathogenic strains of microbes. Their convenient and rapid syntheses along with an effective observed antimicrobial activity make them a very attractive alternative of conventional silver-based products [19,20]. They have also been found to surpress an assortment of cancer cells [21-23]. Moreover GSNPs interact with the immune system and moderate its functioning, causing immunosuppression or immunostimulation depending upon the sizes and surface chemistry [24].

They are shown to be larvicidal against filariasis and malaria vectors [25].

2. BIOLOGICAL SYNTHESIS OF GREEN SILVER NANOPARTICLES (GSNPS)

The contemporary age of unparalleled growth and developments, the indiscriminate use of drugs, followed by rapid spread of antibiotic resistance (AR) and multidrug resistance (MDR) among the microbial community has forced the scientific community to address these grave conundrums through a much greener approach that should help in the fabrication of GSNPs without putting extra burden on the environment. Consequently, the plant leaf extracts of *M. oleifera* [26,27], *C. album* [28], *Citrullus lanatus* [29], *A. indica* [30], *G. mangostana* [31], *M. esculent* [32], *C. annuum* [33], *Geranium* sp. [34], *D. kaki* [35], *Coriandrum* sp. [36], *E. chapmaniana* [37], *C. camphora* [38] , *C. papaya* [39], *V. vinifera* [40], *P. grandis* [41], *O. tenuiflorum, S. trilobatum, S. cumini, C. asiatica*, and *C. sinensis* leaves [42], Carob [43], *N. tobaccum* leaves [44] and many more have been successfully used for silver nanoparticle synthesis. The phytochemicals and compounds present in plant extracts such as alkaloids, proteins, enzymes, amino acids, alcoholic compounds, polysaccharides, quinol, chlorophyll pigments, flavonoid and terpenoid, etc., operate both as reducing and stabilizing agents for the production of nanoparticles [45]. These phytochemicals have been demonstrated to cause direct reduction of silver ions resulting in the formation of silver nanoparticles. Flavones, organic acids, and quinones are water-soluble phytochemicals that are accountable for the instant reduction of the ions as revealed by Prabhu and Poulose, 2012 [6]. They further described the occurrence of emodin, an anthraquinone in xerophytes and three forms of benzoquinones: cyperoquinone, dietchequinone, and remirinin, in which the former was observed to undergo tautomerisation leading to the development of silver nanoparticles. The stability of such silver nanoparticles is usually due to capping of an additional set of phytoconstituents present in the plants extract [46] which prevents the agglomeration of silver nanoparticles and imparts a longer shelf life to the product [12]. The source of the plant extract is identified to influence the characteristics of the nanoparticles [45]. This is because the combination and concentration of organic reducing agents vary in different plant extracts [47]. Characteristically, a plant extract-mediated bioreduction involves addition of the aqueous extract in an aqueous solution of the relevant metal salt. The reaction occurs at room temperature and is generally complete within a few minutes. In view of the number of different chemicals involved, the bioreduction process is however, relatively complex [11] and requires further detailed investigation.

3. MECHANISM OF ACTION OF GSNPS AGAINST PATHOGENIC CELLS

The plant extract mediated silver nanoparticles have been significantly studied for their antibacterial and antifungal aptitudes [12]. Some of the literature illustrated the possible mechanism of antifungal activity as an attribute decided by the size and shape of the silver nanoparticles. Small size nanoparticles having large surface area ensure improved fungal inhibition. Spherical shape with size-reduced silver ions has the increased contact area so that it can eliminate the bacterial growth. Activity of silver nanoparticles has similar effects as silver ions [48]. Positively charged silver ions may attach with negatively charged cell membranes of microbes by electrostatic attraction [49]. Silver nanoparticles form the pits in the cell wall and damage the cell permeability [50] and induce the proton leakage caused by ROS in the membrane [51,52] resulting in cell death. The detailed mechanisms of antibacterial and antifungal actions of GSNPs are discussed in the forthcoming sections.

3.1. Antibacterial activity

The appliance of numerous flora mediated silver nanoparticles has been investigated for their enhanced antimicrobial potential (Table 1, Fig. 1). Though the exact mechanism of action of green Silver nanoparticles (GSNPs) still needs to be surfaced, there are a few theories hypothesized for the same. According to Sondi and Salopek-Sondi, 2004 [49], the antimicrobial action of GSNPs is dependent upon the release of silver ions and free silver radicals in the cellular vicinity [12]. This release of the positively charged silver ions from silver nanoparticles causes electrostatic attraction between positively charged nanoparticles and negatively charged cell membranes of microorganisms [51,69]. After getting accrued the silver nanoparticles subsequently penetrate within the bacterial cells forming pits in the cell membrane [6] of *E.coli*, a gram negative bacteria and accumulation of metal nanoparticles on the bacterial membrane. A mem-

Table 1. Antibacterial properties of green synthesized silver nanoparticles.

Plant Source	Size and Shape of GSNP	Susceptible Bacterial Species	Reference
Acalypha indica	20–30 nm; spherical	*Escherichia coli* and *Vibrio cholerae* (10 microg/ml)	*Krishnaraj et al., [30]*
Allium cepa	33.67 nm	*E. coli* and *Salmonella typhimurium*	*Saxena et al.,[53]*
Arbutus unedo (Strawberry)	*15-25 nm*	*Pseudomonas putida* and *Klebsiella pneumonia, E.coli staphylococcus aureus* and *Bacillus subtilis*	*Naik et al. [54]*
Calotropis procera Leaf and Stem Extract	19 to 45 nm (L) and 26 to 38 nm (S) of facecentered cubic (FCC)	*K. pneumonia* and *S. Typhi*	Gondwal and Pant, [55]
Cajanus cajan	5-60 nm; spherical	*S. aureus* and *E. coli*	Nagati et al. [56]
Carica papaya	10-50 nm; cubic and hexagonal shape	*E. coli* and *P. aeruginosa*	Jain et al., [39]
Catharanthus roseus	48-67 nm	*Bacillus cereus*	Mukunthanan et al., [57]
Cleome viscose	50 nm; spherical	*P. vulgaris, V. cholera* and *P. aeruginosa*	SudhaLakshmi et al., [58]
Eucalyptus chapmaniana	Crystalline with FCC structure	*S. aureus, E. coli, K. pneumonia, P. aeruginosa, Proteus vulgaris*	Sulaiman et al., [37]
Kigelia Africana	13-55 nm	*S. aureus, E. coli*	Suriyamurthi et al., [59]
Matricaria chamomilla	60-65 nm	*S. aureus*	Negahdary et al., [60]
Moringa oleifera	57 nm	*S. aureus*	Prasad and Elumalai, [26]
Ocimum sanctum L.	40-50 nm 4-30 nm	*S. aureus* and *S. Saprophyticus* *S. aureus* and *E. coli*	Das et al., [61] Ramteke et al.,[62]; Singhal et al.,[63]
Ocimum tenuiflorum	28 nm	*E. coli*	Logeswari et al., [42]
Paederia foetida L. leaf extract	24 nm; spherical	*Klebsiella sp., V. cholera, P. aerueginosa*	Madhavraj et al., [64]
Prosopis chilensis	5 to 25 nm, spherical	*Vibrio sp.*	Kandasamy et al., [65]
Rhinacanthus nasutus leaf extract	~11.5 nm; spherical	*S. aureus* and *K. pneumonia*	Pasupuleti et al., [66]
Ceratonia siliqua (carob) L.	5-40 nm	*E. coli*	Awwad et al., [43]
Solanum tricobatum	22.3 nm	*S.aureus*	Logeswari et al., [42]
Solanum xanthocarpum L. Berry Extract	10 nm; mono dispersed helical in shape	*Helicobacter pylori*	Amin et al., [67]
Vitex negundo	18.2 nm	*S. aureus* and *E.coli*	Zarger et al., [68]
Vitis vinifera	1-10 nm	*Bacillus subtilis* and *Klebsiella planticola*	Gnanajobitha et al., [40]
Withania sominifera	5-40 nm	*S. aureus* and *E.coli*	Nagati et al., [56]

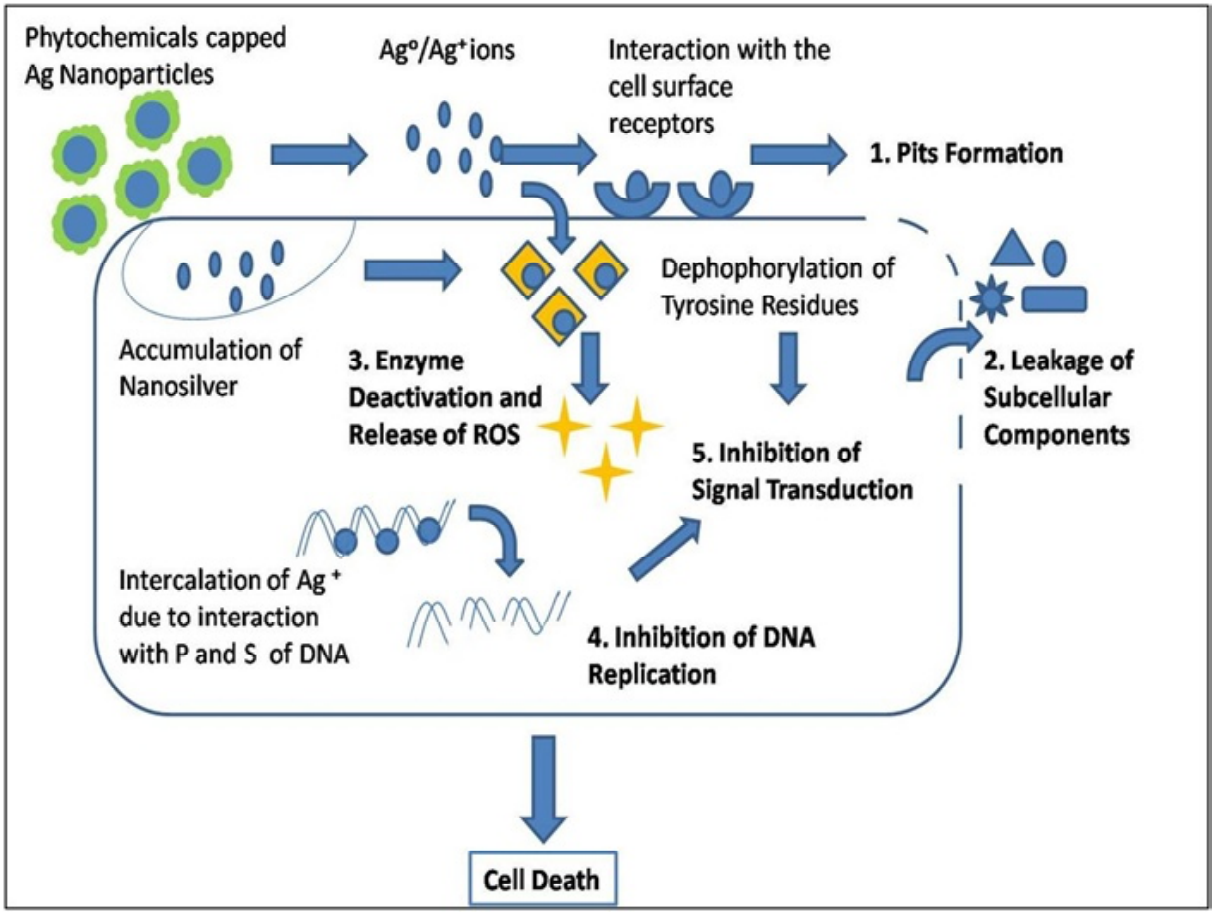

Fig. 1. Diagrammatical representation of the mechanism of antibacterial action of GSNPs including (1) pits formation, (2.) membrane leakage, (3.) enzyme deactivation due to interaction of (Ag^+) with thiol groups of the enzyme, (4.) inhibition of dna replication due to interaction of soft acid (Ag^+) with soft base (P and S) of DNA, (5.) dephoshphorylation of tyrosine residues resulting in the inhibition of signal transduction.

brane with such morphology exhibits a significant increase in permeability, resulting in death of the cell. The formation of free radicals or silver ions by the silver nanoparticles may be considered to be another mechanism by which the cells die [6] which damage the cell membrane and make it porous which can ultimately lead to cell death. These silver ions also interact with the thiol groups of many bacterial enzymes rendering them inactive [70] which in turn restricts various cell processes and overall functioning. According to another theory, GSNPs instigate the formation of reactive oxygen species, which are produced possibly through the inhibition of a respiratory enzyme by silver ions and attack the cell itself. Moreover silver is a soft acid which readily reacts with soft bases naturally present in the form of sulphur and phosphorus containing entities particularly DNA in bacterial cells [71] initiating a chain of events involving problems related to DNA replication and expression, eventually leading to cell death. Besides, the silver nanoparticles have also been found to modulate 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 [6].

3.2. Antifungal activity

Analogous to their antibacterial action, the antifungal activities GSNPs have also been studied (Table 2, Fig. 2). A consortium of studies corroborate the antifungal properties of GSNPs, however the precise mechanism of action is still under cover akin to antibacterial properties. Initial evidence was given by Elumalai *et al.,* 2010 [76] while investigating the antimicrobial properties of silver nanoparticles derived from the leaf extract of *Euphorbia hirta.* The

Table 2. Antifungal properties of green synthesized silver nanoparticles.

Plant Source	Size and Shape of GSNP	Susceptible Bacterial Species	Reference
Artocarpus heterophyllus	-	*Aspergillus niger* and *Pichia pastoris*	Thombre et al., [72]
Dioscorea batatas (rhizome extract)	Monodispersed, circular and flower shaped	*Saccharomyces cerivisae* and *Candida albicans*	Nagajyothi and Lee, [73]
Boswellia ovalifoliolata (Bark)	-	*Aspergillus sp.*	Savithramma et al., [74]
Cleistanthus Collinus	131 nm	*Aspergillus niger, Trichoderma viridae*	VennilaRaj et al., [75]
Eucalyptus chapmaniana	413 nm, face centered cubic structure	*Candida albicans*	Sulaiman et al., [37]
Euphorbia hirta	40-50 nm	*Candida albicans, C.kefyr, A.niger*	Elumalai et al., 2010 [76]
Gelidiella acerosa	22 nm	*Mucor indicus, Trichoderma reesei, Fusarium dimerum* and *Humicola insolens*	Marimuthu et al., [77]
Gracilaria corticata	18-46 nm	*Candida albicans* and *C. glabrata*	Kumar et al., [78]
Matricaria chamomilla	60-65 nm	*Candida albicans*	Negahdary et al., [60]
Moringa oleifera	57 nm	*Candida tropicalis*	Prasad and Elumalai, [26]
Olive seeds	10-30 nm	*Aspergillus niger*	Khadri et al., [79]
Rhinacanthus nasutus leaf extract	~11.5 nm; spherical	*Aspergillus niger* and *A. flavus*	Pasupuleti et al., [66]
Shorea tumbuggaia (Bark) extract	-	*Fusarium sp.*	Savithramma et al., [74]
Svensonia hyderobadensis L. Extract	-	*Rhizopus sp. A. flavus, A. niger, Curvularia* and *Fusarium*	Rao and Savithramma, [80]

produced nanoparticles were found to be effective against yeast *Candida albicans, C. Kefyr* and mold *Aspergillus niger.* A year later, extract of rhizome of *Dioscorea batatas* has been used to synthesize silver nanoparticles [73] having antifungal effects against *Mucor* and *Trichoderma resei*. The nanoparticles were found to be antifungal against the yeasts *C. albicans* and *Saccharomyces cerevisiae.* However tremendous work needs to done in order to surface the definite mechanism of antifungal action of GSNPs. Kim *et al*., 2007 demonstrated that silver nanoparticles inhibit the conidial germination on fungi [81]. On the other hand, microscopic observation revealed that the synthesised nanoparticles caused detrimental effects not only on conidial germination but also on fungal hyphae [82]. Other deformations such as structure altered of the cell membrane and inhibition of normal budding process of both *Rhizopus* sp. and *Aspergillus* sp., have also been observed probably due to the destruction of the membrane integrity [83-84]. The result obtained by Lee and Lee, 2014 suggest that the mechanism of antifungal action of GSNPs may be the release of several intracellular components during the membrane disruption by silver nanoparticles caused by the perturbation of the membrane lipid bilayers, resulting in the leakage of ions and other materials as well as formation of pores and dissipating the electrical potential of the membrane [85].

3.3. Immunomodulatory activity

The studies of immunomodulatory properties of silver nanoparticles produced by green method are scarce. However, the investigations regarding the

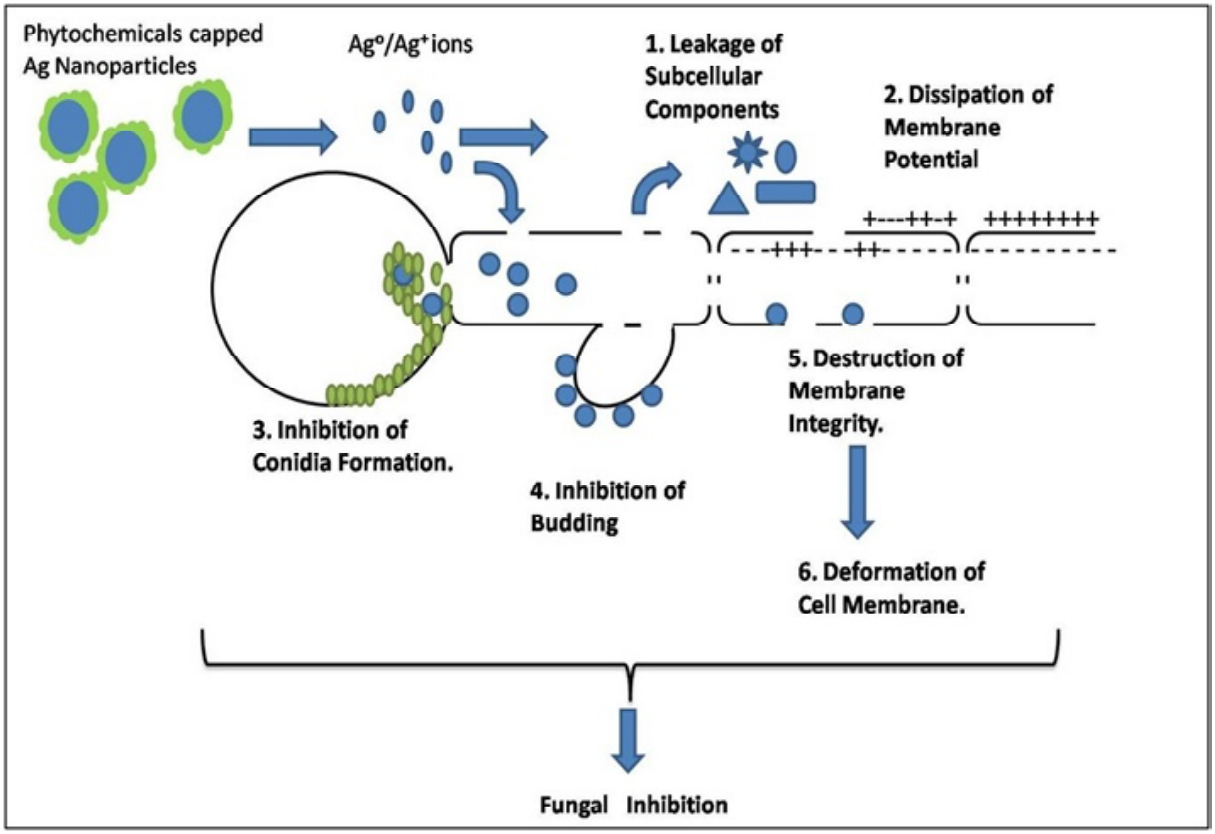

Fig. 2. Diagrammatical representation of the mechanism of antifungal actions of GSNPs including (1) leakage of subcellular components, (2) dissipation of membrane potential, (3) inhibition of conidia formation (4) inhibition of budding, (5) destruction of membrane integrity, (6) deformation of cell membrane.

immunomodulatory properties of usual silver nanoparticles suggest that the AGNPs induce ROS and inflammation [86,87], indicating its potential interference in immune system. AgNPs (22 nm) exposure caused the downregulation of expression of Malt1 and Sema7a genes, which were associated with immune cell function, followed by aberrant T cell differentiation [88]. The toxicity studies revealed a relationship between silver nanoparticles and immune function. Chakraborty *et al*., 2015 assayed the protumorigenic cytokines TNF-α, IL-6 and IL-1β which were found to be down-regulated after treatment with mouse serum albumin coated silver nanoparticles in fibrosarcoma cells [89]. Lappas, 2015 also demonstrated the effective characteristics of silver nanoparticles in relation to immunomodulation and immunotoxic behavior [90]. Silver nanoparticles are easily internalized by cells of immune system and may get accumulated in peripheral lymphoid organs, and stimulate several manifestations in the immune system. Besides similar encapsulation efficiency and the capacity of free radical generation in metal nanoparticles envisage their application as a prospective vehicle for drug/vaccine delivery for macrophages and also implicate towards their immunomodulatory activities [91]. Particularly interesting are the plausible interactions between silver nanoparticles and peripheral blood mononuclear cells (PBMCs). It has been proposed that AgNPs may modulate interleukin 6 secretion mediated by Toll-like receptor (TLR) signaling in macrophages [92], which is recognized as both pro-inflammatory and anti-inflammatory cytokine and regulation of its secretion is imperative during infection and wound healing. Another study has discovered that monocytes may increase release of interleukin 1 as the result of AgNP exposure. Apart from its role in inflammatory response, interleukin 1 influences lymphocyte proliferation and maturation [93]. If these AgNP effects are confirmed in the future, it could open new possibilities in design of modern immunomodulatory medications as well as experimental models for laboratory research. All these evidences strongly suggest an important vent for the scrutiny of GSNPs in the direction of their role in immunomodulation.

3.4. Cytotoxicity and anticancer activities

Cytotoxicity studies revealed that AgNPs have no adverse toxicity and it was found to be safe [94,95]. However, some studies do suggest silver nanoparticles cytotoxicity up to varied levels. AgNPs were found to be significantly more toxic to *THP1* α cells as compared to *J774* cells, which could be attributed to the intrinsic anticancer property of AgNPs. This might be due to small particle size of AgNPs with enormous specific surface area, which facilitated further expression and dissolution of ions, potentially leading to increased toxicity [91]. AgNPs are highly reactive and exhibit oxidative potential and ability to bind with biomolecules like proteins and DNA, resulting in creating the disturbance in the functioning of biomolecules [96]. In another study done by Kandasamy *et al*., 2013, the shrimps fed with silver nanoparticles exhibited higher survival, associated with immunomodulation in terms of higher haemocyte counts, phenoloxidase and antibacterial activities of haemolymph of *P. monodon* which is on par with that of control [65]. Thus, the present study proved the possibility of using silver nanoparticles produced by coastal *Prosopis chilensis* as antibacterial agent in controlling vibriosis. Ag NPs have also been proved to be cytotoxic on the NK cells towards cancer cells as compared to their gold counterparts [97]. In a more recent study, the silver nanoparticles synthesized from seaweed (*Ulva lactuca*) were potently cytotoxic against Hep 2 cell lines and mildly cytotoxic against MCF 7 and HT 29 cell lines. The synthesized AgNPs were found to be a cytotoxic against human (Hep2, MCF7, and HT29) cancer cell lines. Several cytotoxic compounds such as fucoidans, laminarians, and terpenoids present abundantly in seaweed are stated to posses anticancer, antitumor, antibacterial and anti-proliferative properties [98], which aid in the enhanced anticancer activity of GSNPs [99], corroborating the fact that green synthesis of silver nanoparticles augments the level of their medically beneficial properties as it produces phytochemicals capped nanoparticles.

4. OTHER MEDICAL ASPECTS OF GSNPS

Apart from their antimicrobial activity, silver nanoparticles find tremendous application in the medical domain, owing to their small particle size and varied range of structures. The minute particle size renders these nanoparticles the ability to penetrate within cellular and sub-cellular levels. The silver nanoparticles have also been proved to cross the blood brain barrier suggesting their plausible appliance as a vector for drug delivery to brain. Another attribute of silver nanoparticles extensively exploited for medicinal therapies is their anti-inflammatory property due to which they find application in wound healing. According to previous studies, non-healing of wound is caused by higher local matrix metalloproteinase (MMP) and neutrophil activities [100]. Silver nanoparticles are suggested to inhibit the enzyme activity and initiate neutrophil apoptosis thereby reducing inflammation. Besides they are also found to suppress the activities of interferon gamma and tumor necrosis factor alpha which are involved in inflammation. The antibacterial properties of silver nanoparticles add on to the effectiveness in wound healing. Kwan *et al*. showed that in wounds treated with Ag NPs, there was better collagen alignment after healing when compared to controls, which resulted in better mechanical strength [101-102]. Although the studies till date convincingly suggest the candidature of silver nanoparticles as anti-inflammatory agents that can be used for various therapies, the detailed mechanism of anti-inflammatory action needs to be scrutinized more profoundly. In fact, Anticoat is the world's first wound healing dressing developed by Dr. Robert Burrel in 1995, marketed worldwide in the name of Smith & Mathew. Other silver based wound healing medications are Acticoat 7, Acticoat Moisture Control, Acticoat Absorbent, Silvercel, Aquacel Ag, Contreet F, Urgotol SSD, and Actisorb [6].

Silver nanoparticles have been proved to enrich the bone implants by preventing bacterial colonization due to a rapid initial release of silver ions and ensuring rapid developments of silver susceptible mammalian cells, thereby playing important role in bone replacement therapies [103]. Polymethyl methacrylate and ultrahigh molecular weight polyethylene loaded with silver nanoparticles have been used as bone cements and total bone inserts for complete joint replacement respectively [104]. The application of nano-silver induces antimicrobial action and facilitates strength and durability to the joints of the polymer. The antimicrobial properties silver nanoparticles are also exploited to coat the polypropylene based surgical meshes [105] and as disinfectant [106]. It is also believed that most medical treatments such as intravenous catheters, endotracheal tubes, wound dressings, bone cements, and dental fillings can all make use of nanosilver to prevent microbial infections [6,107].

Investigation towards the diagnostic facet of medical appliance of silver nanoparticles reveals their role in biosensing depending upon their plasmonic properties dictated by their shape, size, and the dielectric medium that surrounds them [108]. These nano-silver based biosensors can effectively sense a large number of proteins that normal biosensors find hard to detect. The expression of these proteins can be used for detecting various abnormalities and diseases in the human body including cancer [109]. In fact, Lin *et al*. discussed the role of silver nanoparticle based Surface-enhanced Raman spectroscopy (SERS) in non-invasive cancer detection. The detailed application of silver nanoparticles also persuasively advocate identical and may be enhanced effectiveness of green silver nanoparticles in the medical domain opening a vent for promising research in this direction [110].

5. CONCLUSION AND FUTURE PROSPECTS OF GSNPS

The ability of microbial cells to use genetic modifications as a strategy for better survival and disseminate the changes with the community has given rise to the peril of antimicrobial resistance and multidrug resistance. The antimicrobial activity of silver has been acknowledged and applied since time immemorial. Recent technological advancements in the field of nanotechnology have boosted their action in the form of silver nanoparticles, owing to small size and better applicability. Moreover the synthesis of these silver nanoparticles by the involvement of different plant extracts adds the armor to these silver nanoparticles and aid them further to combat the given more efficiently [102]. The thus produced green synthesized silver nanoparticles (GSNPs) then impede the growth and spread of clinically relevant microorganisms through a number of mechanisms such as cell membrane disruption, pit formation in cell wall, membrane leakage, enzymes deactivation, inhibition of DNA replication, ultimately causing cell death. The resistance against silver has also not yet demonstrated among the microbial populace, since silver nanoparticles target multiple cellular processes rather than concentrating on a single physiological pathway as in case of antibiotics. Moreover, silver nanoparticles have been found to be associated with the modulation of ROS, Toll like receptors, cytokines and inflammation thereby having a crucial impact on immune system. Similarly the green synthesized silver nanoparticles have shown to have promising anticancer activity against various cancer cell lines (Hep2, MCF7, and HT29). The study in the line of locating the anticancer activity is still in the budding phase and requires detailed scrutiny in order to surface the mechanism of anticancer action. Silver nanoparticles also find applications in diagnostic domain of medical science as an agent of biosensing and therapeutic domain as antimicrobial agent, bone cement additives, joint replacement therapies, dental fillings, wound dressings etc. The established applications of silver nanoparticles in these areas strongly advocate the future researches in the analysis of the role of phytochemicals in augmenting their activities in case of green synthesis of silver nanoparticles.

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