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Sources, Applications and Toxicity Mechanisms of Silver Nanoparticles: A Review.

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ABSTRACT

In recent years the application of various nanomaterial especially silver nanoparticles has enhanced in different industries due to their essential antimicrobial as well as other relevant physical and chemical properties. Though these particles have variousvital applications in multiple sectors, there is an increasing concern related to the potential hazards of these nanoparticles to the human health and environment. In recent years, many studies are focussing on the toxicity of different nanoparticles including silver nanoparticles. However, the exact mechanisms, as well as the toxicity contribution from its ionic and nano-form, is still very much unknown. This review aims to present and discuss the various applications and (eco) toxicity of silver nanoparticles to understand the use of these nanoparticles in a safe way. A significant conclusion includes the need for a risk-benefit analysis for all applications and eventually restrictions of the uses where a clear benefit cannot be demonstrated. Thus, the goal of the current review is to shed some light on the various applications as well as to evaluate the toxic effects of silver nanoparticles (AgNPs) on the living organisms.

Keywords: Algae; cytotoxicity; nanotechnology; Nano-toxicity; silver nanoparticles

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INTRODUCTION

Nanotechnology is a pioneering field of science with the capability of transforming modern advances in technology together with various industrial applications. It is frequently used in multipleareas to serve humanity but in parallel excessive applications and unrestrained discharge of different nanomaterials into the environment results in hazards to many living organisms [1]. In recent years due to early acceptance and rapid development in nanotechnology, they pose negative impacts on the environment. Among various engineered nanoparticles, silver nanoparticles (AgNPs) are most widely used nanomaterial in different consumer products due to their antimicrobial property [2]. Silver nanoparticles are particles having at least one fixed dimensions between 1-100 nm, which contains approximately 20-15,000 silver atoms. These particles have changed biological, chemical and physical properties due to the high surface area to volume ratio [3, 4]. Silver nanoparticles have been used in various commercial products including household products, cosmetics, and medical products even in food and textile industries. Recently, the silver nanoparticles (AgNPs) have frequently been used in various applications such as water purification, food preservation and manufacturing of clothes due to its distinctive antimicrobial properties [5,6].

Due to the wound healing property as well as anti-inflammatory and antimicrobial effects ofsilver nanoparticles these particles gradually more exploited in the medical industry [7, 8, 9]. However, before using these nanoparticles in various medical and commercial products, the toxicity of silver nanoparticles must be examined to evade ecological disturbance due to the environmental pollution caused by them. These nanoparticles can enter into the human body through different routes including skin, gastrointestinal tract and respiratory tract. Thekey mechanism of cytotoxicity induced by AgNPs is through the oxidative stress results from the reactive oxygen species generation inside the cells. The distinctive properties of nanomaterials such as chemical, optical, mechanical, magnetic and electrical compared to their bulk materials make them a potential candidate for various application in different industries [10]. Therefore, due to the revolution in nanotechnology, the debate on the toxicity and impact on the environment has been increased [11]. However, the effect of these nanomaterials on the environment and human health is relatively unexplored. Nanoparticle showed toxic effects at cellular, subcellular and bimolecular level. The induction of reactive oxygen species is considered to be a mostcrucial mechanism of cytotoxicity caused by metallic nanoparticles [12]. Increased ROS generation and lipid peroxidation have also been reported in-vivo under AgNPs exposure. The enhancement in ROS level results in DNA damage, necrosis and apoptosis [12].Thus, present review aims to highlight and discuss the application and underlying toxicity mechanisms of AgNPs.

SILVER NANOPARTICLES (AgNPs)

Silver(Ag) belongs to the 'd' block in the periodic table and is an element of group 11 and period 5 withstandard atomic weight 107.862 and atomic number 47. The density of silver is approximately 10.49 g/cm^3, its oxidation state is +1 and the atomicradius of about 145 pm. It has high electrical and thermal conductivity as well as high reflectivity. Silver in nano-form, i.e. AgNPs, also have distinct chemical and physical properties such as catalytic activity and non-linear optical characteristics. AgNPs contain around 20–15,000 silver atoms [13] and their size ranges from 1-100nm.These nanoparticles are found in different shapes such as spherical, octagonal or the form of sheets, rod-shaped, cylindrical shaped, wire-like,plate-like, and belt-like etc. [14, 15, 16].

Silver is used in various clothing items including many sports clothing such as T-shirts, socks, undergarments and many others. Due to it being a potent inhibitor for a broad spectrum of antimicrobial activities, such as those of bacteria, fungi, and viruses, it is widely used in medical field for dental hygiene, wound dressings, treatment of eye illnesses and other infections as well [17]. It has been confirmed that Ag^+ ions, a prototypical antimicrobial silver species in the form of a silver nitrate solution, are active against a wide range of bacteria and fungi [18]. Compared with other metals, silver shows higher toxicity to microorganisms while exhibiting lower toxicity to mammalian cells [19]. Additionally, it has been revealed that silver can bind to the DNA, increasing the decomposability of genomic DNA[20] or inactivating the respiratory chain thereby inducing the formation of hydroxyl radicals inside the cells[21].

SOURCES OF SILVER NANOPARTICLES

The substantial amount of AgNPs is present in our environment due to various natural as well as anthropogenic activities, which may have a negative impact on the environment [22, 23]**.** AgNPs may have been deposited into the soil after the reduction of Ag^+ ions by dissolved organic matter in natural water [23] or may have been formed after oxidative dissolution and subsequent decrease of various silver objects [23, 24], which are then released into the surroundings during washing or disposal of these objects[24, 25]. Although AgNPs are found naturally, there should be no doubt that anthropogenic activities play a crucial role in silver nanoparticles pollution in the environment. Theuse, as well as synthesis of NPs in various industries, contributes one of the most prominent anthropogenic sources of AgNPs in the environment [26]. The methods used for NP synthesis are usually non-eco-friendly as they use various strong reducing and stabilising agents [26,27]. These engineered NPs are released into the soil in the form of metals, dust etc. The AgNPs released from anthropogenic sources are of greater concern as they contaminate the environment directly. AgNPs are being used in various electronic devices, medical devices, in textiles or are addedtomanydisinfectants, all of these sources result in the direct discharge of AgNPs into the environment [24]. Inappropriate disposal of biosolids or wastes, spills and other organic fertilisers or pesticides also results in the release of these NPs[16,28].It is assessed that about 500 tons per annum of AgNPs are being produced, which is exponentially growing every year. An overview of various sources of silver nanoparticles in the environment is shown in **Fig. 1**[1].

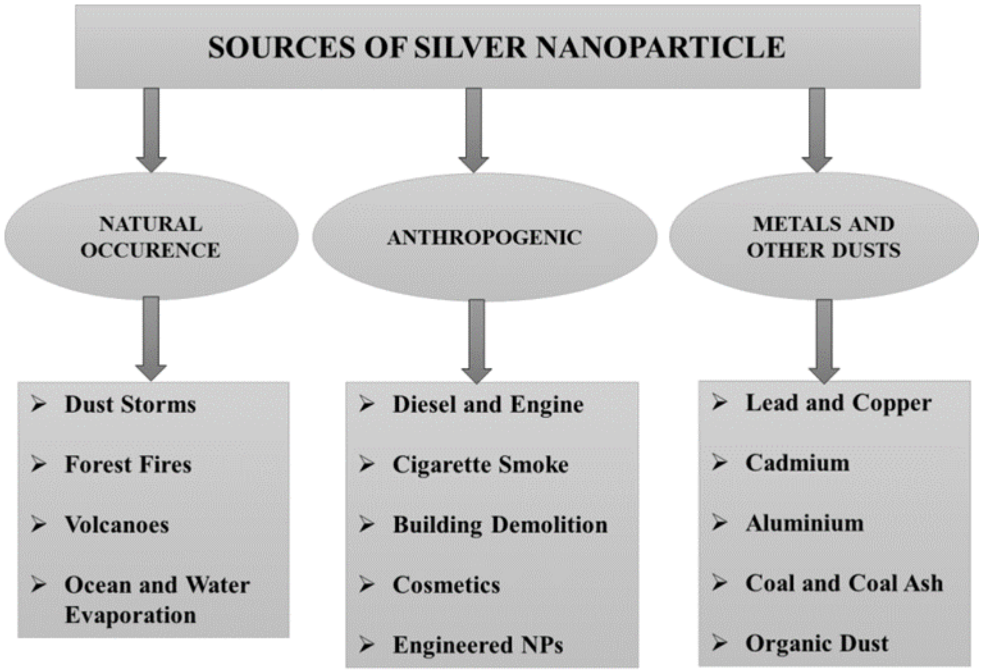

Figure 1: Sources of Silver Nanoparticles [1]

APPLICATIONS OF SILVER NANOPARTICLES

AgNPs have found to be used in more than 250 consumer products in the world [16]. There is multiple application of AgNPs have been found in various sectors including commercial and industrial region as well as in the field of bioremediation and biomedicine owing to its characteristic physiochemical properties [29,30]. Due to their various commendable properties such as anti-microbial, anti-fungal, anti-fungicide, anti-viral along with properties like electrical conductivity and localised surface Plasmon resonance effect, these particles have extensive application in numerous fields. **Fig. 2** outlines the various applications of AgNPs in different industries and sectors.

Its anti-microbial property has led to it being used in as an antibacterial coat in medical applications such as dental composites, wound dressings, catheters, orthopaedic implants, and also in the cardiovascular implants.

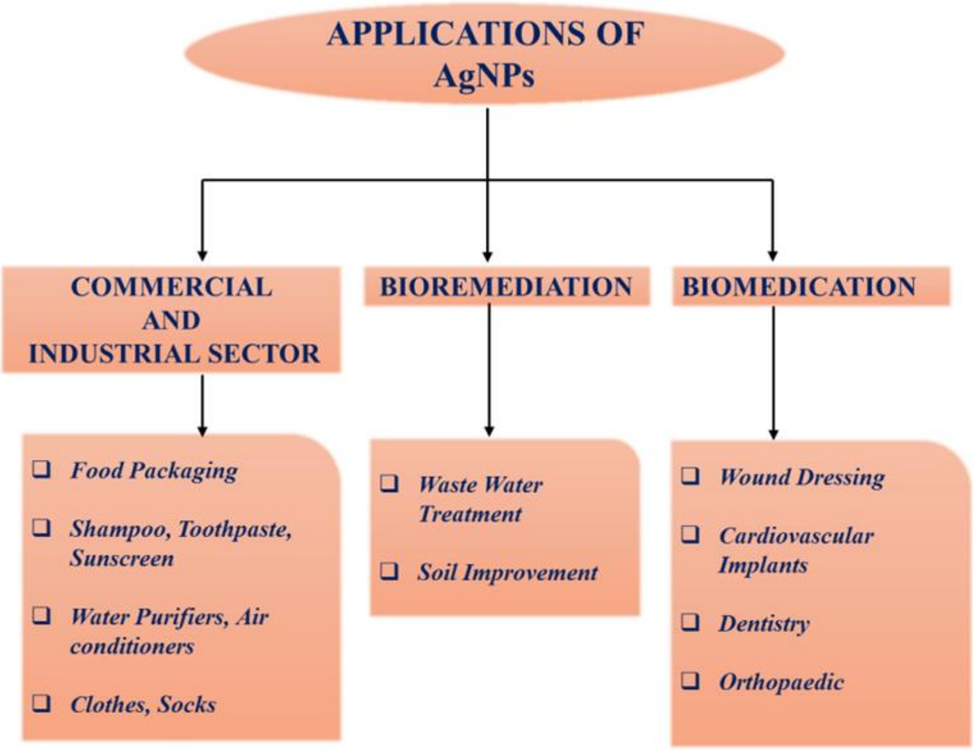

Figure 2: Applications of Silver Nanoparticles

Wound Dressings

Silver has been used in wound dressings from over 100 years to clinically treat various wounds, such as burns, chronic ulcers, toxic epidermal necrolysis, and pemphigus [29]. Interestingly, wound dressings containing AgNP significantly decreased wound healing time by an average of 3.35 days, simultaneously these particles also promote bacterial clearance from the infected wounds that too without any adverse effects in comparison to standard silver sulfadiazine and gauze dressings.

Cardiovascular Implants

Heart valve was the first cardiovascular device to be coated with the silver element, itwas donetoreduce the occurrence of endocarditis, a prosthetic silicone. Silver was used owing to its antibacterial properties, thereby preventing the bacterial infection on the silicone valve and consequently reducing the inflammation response of the heart. However, in the clinical trials of the silver heart valve found that silver causes hypersensitivity inhibits normal fibroblast function, and leads to para valvular leakage in patients. Thus, to combat this toxicity of silver, scientists focused on incorporating AgNPs into medical devices as a potential for providing a safe, non-toxic, antibacterial coating.

Catheters

Catheters which are used in the hospital have a high propensity for infection, which can lead to unwanted complications. Therefore, for reducing biofilm growth on catheters, a strategy of using AgNPs have been investigated. Recently, to produce antibacterial catheters, AgNPs has been used to coat polyurethane catheters. Various studies have reported that AgNP-coated catheters can effectively reduce bacteria for up to 72 hours in animal models [31, 32]. Furthermore, a follow-up 10-day in vivo study in mice confirmed that the AgNP-coated catheter was nontoxic.

Dentistry

AgNPs have also been used inthe bandages and dental instruments. Akhavan et al.also demonstrated in their study that the shear bond strength of orthodontic device can be increased or at least maintained by incorporating AgNPs into it, and consequently increasing its resistance to bacteria [33].

Orthopaedic and Orthodontic Implants and Fixations

One of the most severe complications in orthopaedic surgery are implant associated and joint replacement bacterial infections which are high at 1.0–4.0%, it is because they are adamant to treat and result in increased morbidity and considerably worse outcomes [7,34]. Thus, as a way to reduce bacterial resistance, AgNPs have been incorporated into plain poly(methyl methacrylate) bone cement, used for the secure attachment of joint prostheses hip and knee replacement surgery.

In Research

AgNPs are also being frequently used in the many research fields such as, in sensing and imaging applications, including the detection of DNA, selective colourimetric sensing of cysteine, sensing purine nucleoside phosphorylase activity and selective colourimetric sensing of mercury(II) as well [35].

Fungicide and Antiviral agent

Apart from being used as for its anti-microbial property. Nanosilver is also used as an efficient fungicide against several fungal strains, such as *Aspergillus fumigatus*, *Mucor*, *Saccharomyces cerevisiae*, and *Candida tropicalis*[15] as well as for its antiviral properties which can be used against the HIV, hepatitis B and Herpes simplex virus [36]. These NPs are also used in many diagnostic applications, such as in making nanoprobes and in antibiotics such as nano-gels and nano-lotions [37-40].

Other Applications

Various example of AgNPs being used in our day to day life is present, like, in bedding, washers, toothpaste, shampoo, food packaging materials, food storage containers, water purifiers, odour-resistant socks, room sprays, laundry detergents, etc.

Recently, the Project on Emerging Nanotechnologies at the Woodrow Wilson International Centre for Scholars has found a list of more than 400 consumer products that claim to contain nanosilver [41]. Due to the increasing use of AgNPs in several commercial products as discussed above, the potential for the release of these NPs into the environment and its effects on environmental health are of increasing concern [9, 41-47]. Owing to the vast array of applications of these NPs, they can interact with the environment frequently at a large scale. Thus there is raising concern about its toxic effects on the atmosphere over a period.

TOXICITY OF SILVER NANOPARTICLES

Research spanning several years have identified that AgNPs can cause damage to various cellular components including DNA, protein and lipids. Which further leads to DNA damage, activation of antioxidant enzymes, depletion of antioxidant molecules (e.g., glutathione), binding and disabling of proteins, and damage to the cell membrane [48].Transformation of any substance specially nanoparticles in biological and environmental media play an essential role in determining their toxicity towards environment, same is the case with nanosilver where NPs toxicity is evaluated by its transformation in different media, which can further lead to its surface oxidation, release of silver ions, and interaction with various crucial biological macromolecules [42, 44, 45, 49,50].

UNDERLYING TOXICITY MECHANISM OF SILVER NANOPARTICLES

A characteristic feature of nanosilver is its ability to interact with cellular membranes and thus causing toxicity.The mechanism behind its antimicrobial effect is also stated due to its ability to communicate with bacterial membrane [51-53]. The ionic and non-ionic form of AgNP exerts their toxic effects chiefly by interacting with macromolecules containing sulfur such as protein, as silver has shown a strong affinity towards sulphur [48, 54-59]. But estimating whether a particular portion of nanosilver toxicity is from an ionic form or non-ionic form is still a challenge [12, 60-62].The toxic effects of silver nanoparticles are summarised in **Fig. 3**.

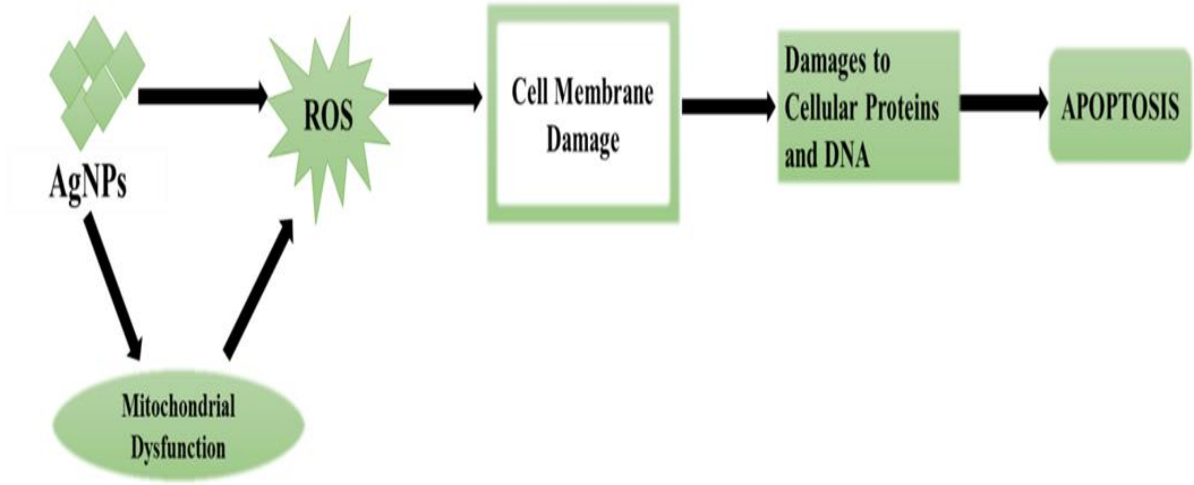

Figure 3: Toxic effects of Silver Nanoparticles [105]

Cytotoxicity of AgNPs is found to be due to the cellular uptake of these NPs, which further induced ROS generation and escalation of cellular antioxidant mechanisms [60, 63-73]. The AgNPs enter the cell through diffusion or endocytosis leading to mitochondrial damage, which further leads to the generation of the massive amount of reactive oxygen species (ROS).When the cell lacks enough energy to accelerate the antioxidant defence system to combat these ROS, then it leads to the oxidative stress inside the cells [63, 68, 71, 72, 74]. These ROS mediated oxidative stress then cause damage to major biomolecules including proteins and nucleic acid, thereby inhibited cell growth [68, 71, 74-79]. The underlying toxicity mechanism of AgNPs is shown in **Fig. 4**.

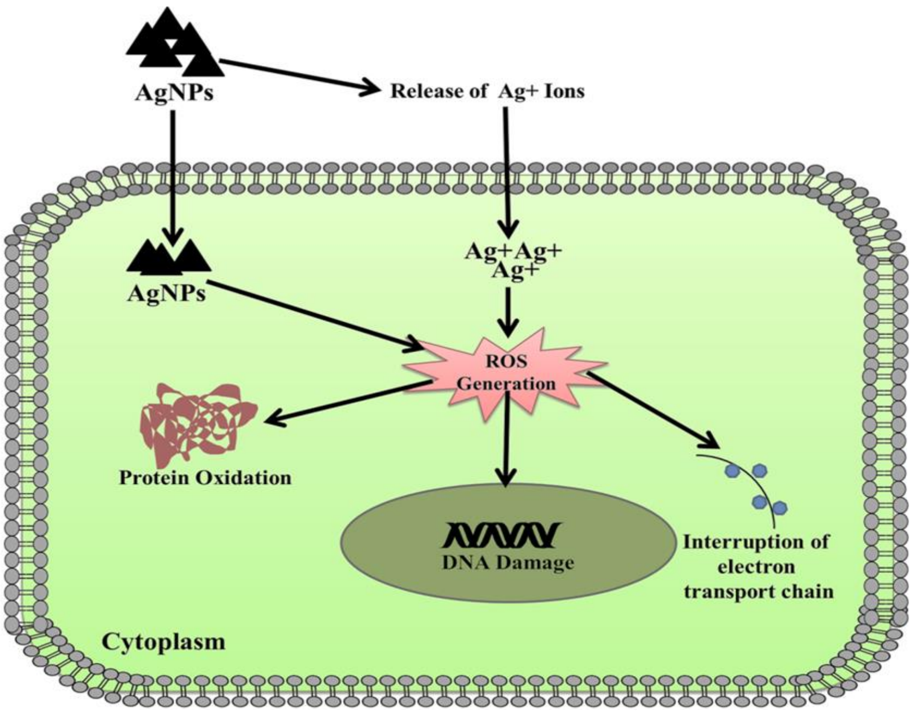

Figure 4: Systematic representation of underlying toxicity mechanism of AgNPs

The evaluation of AgNP toxicity has been doneon some marine and freshwater phytoplankton in many studies[80-85]. The toxicity of AgNPs towards the phytoplankton is mainly due to the release of Ag^+ from AgNP either within their growth medium or after the uptake of NPs into the cells as stated by many research groups[86-88]. The underlying mechanism of AgNP toxicity is that the cations play an important role in a variety of cellular processes and though phytoplanktons have well-established mechanisms to control the uptake and storage of metals, they sometimes fail to discriminate between essential and non-essential cations,for example, Ag^+.Hence uptake of undesired metal leads to various complication such as rendering protein and alterations indifferent metabolic processesof the cell.Simultaneously, it has also been stated that the release of Ag(I) cannot be solely attributed for the AgNP toxicity [83, 89-91], as the overall toxicity of AgNP towards phytoplankton is the cumulative result of reduction of light availability due to adsorption of NPs on the cell surface [81, 92] and also due to the enhanced presence of exopolymeric substances (EPS) [86, 93]. The studies related to the effect of AgNPs is not only limited to phytoplankton but has also been carried on other aquatic species such as autotrophs, mainly algae.

INTERACTIONS BETWEEN SILVER NANOPARTICLES AND ALGAE

AgNPs are being frequently used in many industries as well as household products, which lead to the discharge of the substantial amount of these NPs into the water bodies. AgNPs are also employed in wastewater treatments which results in the accumulation of significant amount of NPs in water bodies overtime, thereby affecting the aquatic organisms including algal species, as these species stand in the first line in the aquatic ecosystem. Aquatic microorganisms such as algae and cyanobacteria play an important role in nutrient cycling and the health of freshwater ecosystems. They are amongst the most sensitive species to the toxicants. Therefore, these organisms are being repeatedly used in various risk assessment and fate studies.

Algae are mostly aquatic and are polyphyletic eukaryotic autotrophs, as they have tissues and cells like xylem and phloem which helps them in making their food. They can be found in unicellular as well as multicellular forms. These organisms are important part of aquatic photosynthesis and aquatic food chain, are also being exploited in a wide range of industrial applications [94]. However, the toxicity data related to the effects of NPs on various algal species are still sporadic, due to the different and variable growing conditions of these organisms. Thus, the evaluation of the impact of AgNP on these photosynthetic organisms is a vital aspect of current research.

UPTAKE

The algal cell wall is composed of carbohydrates, protein and cellulose that form a stiff elusive network, which acts as a semi-permeable sieve and allows only small particles inside the cell and obstruct the transport of larger NPs. AgNPs are often able to transit through the pores of cell wall due to their large surface area and small size, and then they can finally reach to the plasma membrane [95]. Sometimes the transport of AgNPs through the pores of the cell wall is aided by various processes such as cellular reproduction, which enhanced the cell wall permeability due to newly fabricated pores. The cell wall of different organism has a different affinity, and non-specific interactions with silver ions due to the difference in their biological makeup, i.e., cyanobacterial cell wall consists of particularly peptidoglycan whereas green algal cell wall is mainly made up of cellulose [96]. Many studies have investigated that average cell wall size of algae and cyanobacteria ranges from 5 to 20 nm, through which a single NP can pass quickly. The interactions between the cell wall and NPs lead to the damage to the pores, which in turn increased the pore size large enough to make larger particles accessible through this, consequently expanding the internalisation efficiency of the cells. AgNPs can make their way to enter the cells using various ion channels or transport carrier protein. AgNPs can also encompass in cavities like the structure fabricated by plasma membrane and then can be easily imbibed into the cell through endocytic processes [97].

EFFECT OF SILVER NANOPARTICLES ON ALGAL CELL FUNCTIONING

Properties of nanoparticles (concentration, size, stability, morphology, and aggregation state), the surrounding medium (composition, concentration of suspended and dissolved species) and the interactions between these two are likely to affect their exposure and toxicity to microorganisms. Many studies have recounted the adverse effect of Ag on both freshwater and marine algae [46, 88] with effective concentrations ranging between 1 µg Ag/L [57] and up to 75 mg Ag/L. Many laboratory-based experiments have also demonstrated that AgNP showed toxicity towards algal species [65, 94]. These NPs can enter the organism through the cell wall, thereby causing damages to the cell membrane, loss of membrane integrity and finally leads to cell death [70, 98-100].

AgNPs affects the multiple structural as well as functional properties of algal cells by inducing severe alterations such asa decrease in chlorophyll content, viable cell counts, increased ROS generation and lipids peroxidation (MDA) [40, 65, 70, 86]. AgNPs exposed to dissolved oxygen can result in the formation of oxygen free radicals at the surface, which further leads to the oxidative stress inside the cells. When AgNP enters the cell, it gets attached to various cell organelles and caused a disturbance in their metabolic and biochemical functions by augmenting the ROS generation, which can be assessed by the occurrence of multiple symptoms such as swelling of the endoplasmic reticulum and vascular changes [86].The other negative impact of AgNP has also been seen on algal reproduction [101, 102], photo system II (PSII) photochemistry, alteration of the oxygen evolution complex, inhibition of electron transport activity, and structural deterioration of PSII reaction of the green algal species [81, 103]. These NPs also affect the photosynthetic and respiratory processes of various photosynthetic organisms.

DEFENCE AND TOLERANCE MECHANISM

Algal species possess various tolerance mechanisms to combat the primary effects posed by the AgNPs. Concentration and exposure duration are the significant factors determining the durability of the effects and also the negative impacts on the algal species. Microalgae and cyano bacteria have enzymatic and non-enzymatic oxygen scavenging defence mechanisms to prevent the ROS mediated damages to various cellular components. However, understanding the whole defence mechanisms in the algal cell is a bit challenging in the arena of research, due to the complex ecological condition in which they live and diversity in themselves, which directly affects the adaptation as well as tolerance mechanism of different algal species [104].

CONCLUSION

Nanotechnology has established itself as a science of extensive application in various fields in the modern era, however, controlled and balanced use and most importantly safe disposal methods of nanoparticles is yet to be shaped. Among all metallic nanoparticles, silver nanoparticles are used extensively in the day to day items due to its vital anti-bacterial, antifungal, anti-viral and anti-inflammatory property, but its impact on the environment is yet to be fully investigated. Although various studies are being conducted to determine the toxicity and tolerance of NPs on algae, plants and microbes, no adequate work is being carried out at cellular/molecular level to understand the underlying toxicity mechanisms of AgNPs and other nanoparticles as well. Different studies showed different results causing ambiguity in the toxicological data interpretation. Although much research has been documented related to the toxicity of AgNPs, still there is no defined and optimised level or lethal level of NPs which can cause toxicity to the living organisms at different levels. Silver Nanoparticles and its effect on our environment is a vast field with still little understanding of how these NPs affects our surroundings. Hence there is a need for a common platform which can accumulate all the data and give a logical result to safeguard our environment and humanity. An important conclusion includes the need for a risk-benefit analysis for all applications and ultimately limiting the applications where a clear benefit cannot be revealed.

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