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Review

Ecotoxicological assessment and dermal layer interactions of nanoparticle and its routes of penetrations

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ABSTRACT

Our review focused on nanomaterials-based toxicity evaluation and its exposure to the human and aquatic animals when it was leached and contaminated in the environment. Ecotoxicological assessment and its mechanism mainly affect the skin covering layers and its preventive barriers that protect the foreign particles' skin. Nanoscale materials are essential in the medical field, especially in biomedical and commercial applications such as nanomedicine and drug delivery, mainly in therapeutic treatments. However, various commercial formulations of pharmaceutical drugs are manufactured through a series of clinical trials. The role of such drugs and their metabolites has not met the requirement of an individual's need at the early stage of the treatments except few drugs and medicines with minimal or no side effects. Therefore, biology and medicines are taken up the advantages of nano scaled drugs and formulations for the treatment of various diseases. The present study identifies and analyses the different nanoparticles and their chemical components on the skin and their effects due to penetration. There are advantageous factors available to facilitate positive and negative contact between dermal layers. It creates a new agenda for an established application that is mainly based on skin diseases.

Contents

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1. Introduction

The role of nanoparticles has been studied for various application with their specific interaction optimised with the different dosage levels. The uptake mechanism of an organism significantly measures nanoparticle's exposure. The route of administration by organism identified through different sources such as industrially or pharmacologically derived bulk and nanosized materials; these are widely investigated for the exposure to the human being upon natural and unnatural processes. The possible interaction between skin and dermal layers of the human systems were studied for the external absorption by the tropical applications. Nano and bulk formulation of drugs are currently used for medical treatments to assess the toxic behaviour and its negative influence on tissue matters. The influence of bio-resistant and biodegradable materials, namely liposome and polymeric materials, in skin covering have attained importance in the control mechanism as a biologically derived system (Ahamed et al., 2008). This review is proposed to study the interaction of nanoparticles onto the skin surfaces and its oral exposure with the possible routes of administrations to determine the toxicological responses through human-made and environmental exposures as explained in the schematic shown in Fig. 1. The skin reacts as a supreme preventive layer from the dangerous exogenous or micro-sized toxicants with possible exposure to the various contaminants (Ahamed et al., 2008; Arora et al., 2012; Atiyeh et al., 2007).

The direct delivery of the nanomaterials easily penetrated through the skin appendages because of the smaller size for the transportation of the materials. The intended exposure of drug treatment and creams also participate in the same process. As a sample, the penetration of Silicon dioxide (SiO_2) nanoparticles, with 20–100 nm in size range, was tested with the average human

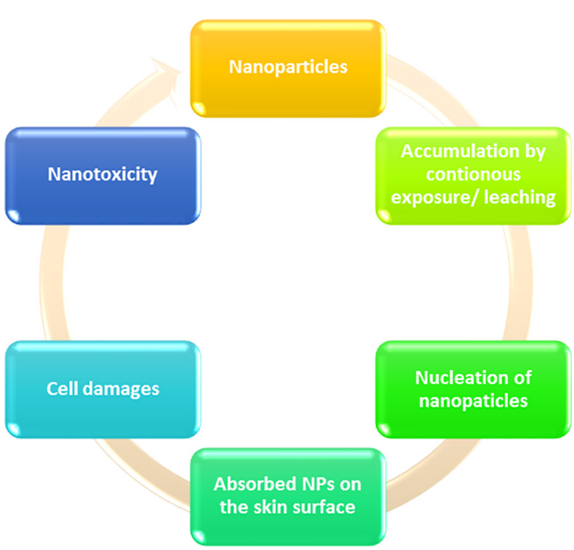

Fig. 1. Flow chart of nanoparticles routes and its interaction mechanism.

skin and grafted human skin sample to penetrate titanium dioxide (TiO_2). The study showed the penetration till the topmost 3–5 corneocyte layer of the stratum corneum (Atiyeh et al., 2007). However, according to the author, some have failed to penetrate the skin with experimental relevance (Simko et al., 2010; Benn and Westerhoff, 2008). Magnesium oxide and TiO_2 can penetrate the human skin dermatome and are failed to penetrate the inner skin layer. The uses of silver (Ag) nanoparticles have been increased in various forms. Moreover, the commercial application of nano silver utilisation in various cosmetics, medicines, sports goods, pharmaceutical applications, electronics, and many direct and indirect human needs is used. The overexposure and continuous demand made it more essential for human exposure.

2. Types of nanoparticles and their penetration

Skin tends to be the natural preventive layer that protects against transdermal and topical drug delivery systems, hence avoiding this difficulty and raising the penetration of particles via the skin. Few other techniques used nanosized drug carriers such as liposome and other vesicular systems are used in nanoparticulate delivery systems (Arora et al., 2012). The utilisation of chemical enhancers does the penetration of particles. Two important routes have been identified to the penetration of drugs: *trans*-epidermal and *trans*-appendageal. These are mainly involved in the drug penetration mechanism through the stratum corneum by multicellular barriers.

There are many techniques used to enrich the penetration of skin, the injectors, micro needles, iontophoresis, electroporation, magnetophoresis, laser irradiation, and ultrasound are the techniques available for the physical and mechanical drug penetrations through the skin. Sometimes, chemically mediated, and biogenic nanomaterials will cause some deleterious effects when they have been used for a more extended period without studying the structural and functional properties, such nanoparticulate may induce various adverse effects such as allergy, cell to DNA damage and cancer depends on the characteristics and functions of the nanomaterial (Ahamed et al., 2008). The behaviour of the nanomaterial can be changed where it shows an effect on protein behaviour. Appendages and intercellular route are the two possible methods. However, there is no substantial proof for the penetration of materials passing the underlying tissues through the upper skin layer. The only way to enable healthy skin penetration is attained by quantum dot (Benn and Westerhoff, 2008). These reports have mainly used various animal skin-based nanoparticles, namely quantum dot, silver, titanium dioxide, and quantitatively measured for the pointed exposure and cellular response on humans (Buzea et al., 2007).

3. Possibilities of exposures

Silver nanoparticles possess the property of antiseptic. In general, they are possessed with biological, physical and chemical properties to behave as a better process initiator, especially when present in the range of nanoscale (Comfort et al., 2011). Since few solid lipid nanoparticles generally have valuable properties, they are used in cosmetic products, textiles, and antiseptic cream. The tropical materials have some advantages, but they produce reactive oxygen species (ROS) and AgNPs responsible for assessing the nanoparticle absorption by in-vitro permeation study by static cell diffusion utilising human skin (Ahamed et al., 2008). Using this technique, we can measure the quantity of silver quickly penetrating per day. In this process, Transmission Electron Microscope identifies the location where silver nanoparticles are present in the skin (Cowan et al., 2003). In many cases, the lower amount or the prescribed doses of silver mediated drugs do not cause any penetration through cells, and it does not affect the system which was exposed for the treatment process. Silver salts have treated disorders related to brain and nicotine addiction.

Silver nanoparticles are an excellent antimicrobial agent in their current state, particularly for many gram-positive and negative pathogenic organisms. These resulted in the effective antimicrobial property opposing 650 types of pathogens that cause disease. In contrast, it did not expose any impact in mammalian cells (Cummings et al., 2013; Desai et al., 2010). Since it changes the membrane stability (Fung and Bowen, 1996). Researchers reported *Escherichia coli* for the sensitivity test and observed excellent antimicrobial effects with varied measuring of silver nanoparticles (Gozes & Shioda, 2012). It has been termed an effective bacterial agent when the AgNPs concentration is above 60 μg/mL. This proposal also contains details about zebrafish embryos and Escherichia coli; it was performed in in-vivo and in-vitro with the known concentrations of silver nanoparticles. More effectiveness was noted in vitro condition than in vivo condition (Gratieri et al., 2010).

Silver nanoparticles lead to the accumulation of ROS; further, it induces inflammatory responses and cell damage. The antioxidant defence mechanisms possessed in the underlying membranes of mitochondria when it undergoes cross collision with other substances like thiol and results may lead to apoptosis (Gozes & Shioda, 2012) in the cytotoxic behaviour. The large surface area to volume ratio showed an excellent antibacterial property using AgNPs, which results in good interaction with microorganisms (Gratieri et al., 2010; Horstkotte and Bergemann, 2001).

3.1. Interlinkage of dermal barrier with silver

The role of silver nanoparticles in the dermal layer of the skin layer has been investigated due to the antimicrobial efficacy of silver nanoparticles. These silver formulations have been used extensively against various treatments and therapies like wound healing and wound dressing, which can also be used against external infections and a chronic ulcer (Kearns et al., 2009; Kulthong et al., 2010).

Silver nanoparticles show observable effects in microorganisms by slowing down the virulence actions due to the size of silver salts ranging from 100 nm, which contains about 20 to 15,000 (Horstkotte and Bergemann, 2001). In those cases, interlinkage of nanoparticles with the internal and external layers of skin can be identified through the skin lesion, and skin surfaces that are damaged can cause pain to humans and animals (Comfort et al., 2014). Therefore, AgNPs have also been injected as topical antibacterial agents are marketed for various uses. Nowadays, they have the specific advantages of resulting controlled release of nanocrystalline silver onto the wounded site (Labouta & Schneider, 2013; Lansdown 2006). Hence the defective skin layers do not expose the effective process in preventing it from other wounds or not as a better protective layer because it can easily go through the particles as well as nanosized particles during the reaction, so it is also a way for penetration of particles (Desai et al., 2010).

The nanosized particles contact and penetration is primarily linked with the structure of the particles, which sizes about 6 nm. The metallic particles of this range can smoothly penetrate through the skin (Comfort et al., 2014). The radius about 7 to 20 nm smoothly penetrates the pilosebaceous sweat glands and pores; this layer of hair follicle infundibulum and its calculation of measured radius is about close to 40 nm also pass through the dermis of perifollicular. Except for silver metallic particles, which go through quickly on the hair orifice and stratum corneum with a dimension range of 10 nm, generally, the layer of human skin is denser than other parts. Hence this particle penetration is not a preferable way in such conditions. Denser skin participating in modifying the softer skin is easy to go through by using colloids (Cowan et al., 2003). The upper stratum of the dermis layer reacts, but it does not enrich the skin permeation (Gratieri et al., 2010).

3.2. Penetration of silver nanoparticle through the skin

The general way of nanoparticle exposure is to the skin through the penetration of different follicles and skin layers; it is considered the principal source for tropical nanoparticle delivery. In silver nanoparticles, the exposure has specific benefits to the precise level for the optimal quantity implementation through antibacterial clothes and medicines. Various incorporated systems are produced in textiles etc. These reactions to the skin protect the outer layer of the body to prevent the invasion of bacteria. In between many metal nanoparticles, silver nanoparticles use harmful effects when it is acute with their highest dose and however it causes harmful effects. It has been researched as the most intensified toxic to mammalian cells; in addition to this nanoparticle which is termed as the most poisonous to the germline stem (Gratieri et al., 2010). The toxic quality of AgNp may be attained from several sources, which may affect the living organisms in ecological and aquatic systems cause symptoms of abnormalities because of the deposition of silver. Consuming and constant external and internal exposure of Ag or Ag derived nanoparticle toxicity depends on their surface chemistry (Gratieri et al., 2010; Larese et al., 2009).

4. Impact on the aquatic environment

These metal nanoparticles, especially the silver-coated textiles and fabrics, enter the aquatic environment while washing; this may contaminate the aquatic environment by releasing synthetic chemicals and nano-coated metal ions, nanoparticles. These cause a negative influence on the environment and may lead to various levels of gene mutation and toxic effects on the aquatic organisms through their diet. Also, it influences the growth and development of valuable microorganisms, which are essential to the various flora and fauna; thus, it affects the algal photosynthetic capacity. This can also induce abnormalities in a wide range of aquatic communities or organisms like fishes, plants and marine bioactive metabolites, as shown in Fig. 2 (Gratieri et al., 2010; Lee et al., 2007; Marx & Barillo 2014).

Continuous delivery of silver nanoparticles into the surroundings may disturb the ecology. Various types of nanosized particles and its result have effects all over the body that are concluded through different clinical trials of conducted studies. The absorption of these particles causes few defects compared to other particles, which cause harmful effects to the other body parts in the human body (Maynard et al., 2011).

This penetrating property takes place in two different systems by two various sources like human skin and animal skin such as pig, rat, mouse based on their working ability when focusing on the tropical diet of the aquatic animals. These aquatic animals

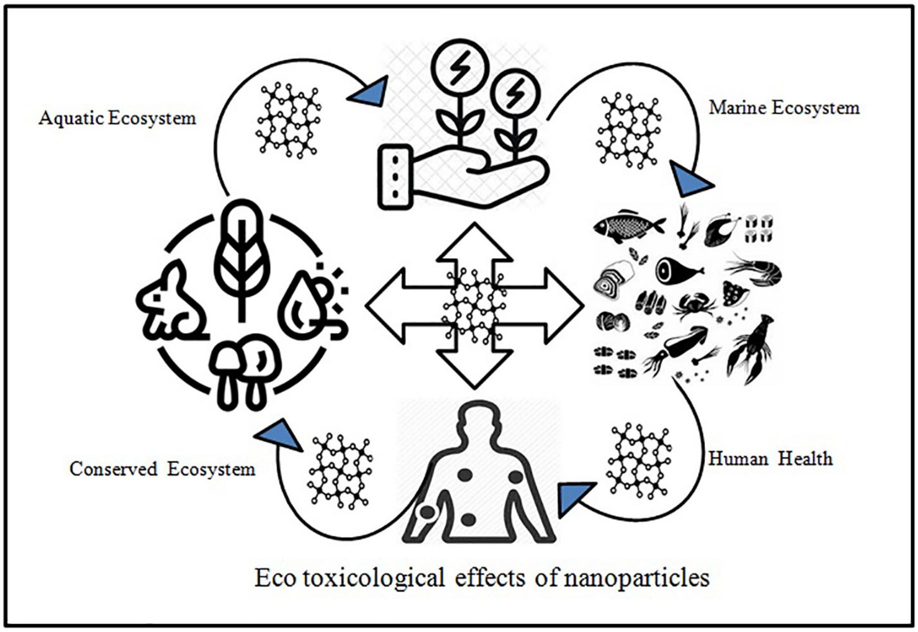

Fig. 2. Ecotoxicological effects of nanoparticles.

are possessed and exposed to various aquatic contaminants. Such pollutants internalised through the uptake mechanism led to the various cytotoxic and genotoxic effects in their genetic patterns. Such metal pollutants are transferred to the human beings who consume the aquatic weeds and animals; this, in turn, leads to the easier chance of penetration to a human with their direct contact through the consumption. This type of contamination can be assessed with the human samples for exposure of different organs.

Human skins are generally not ready for experimentation, but in-vivo and in-vitro conditions are achieved; moreover, comparison in-vitro is better over *in-vivo*. Few characteristic changes in the skin layers of humans and animals, which depend on two conditions, such as morphology and structural difference, like human skin, are more complex compared to animals (Horstkotte and Bergemann, 2001).

Silver nanoparticles tendency can be identified through the Transmission Electron Microscopic (TEM) in vitro analysis result suggesting that penetration happens through the human skin (Ahamed et al., 2008; Gratieri et al., 2010). This TEM analysis revealed the confirmation of the polyvinylpyrrolidone coated poly-dispersed particles have penetrated the SC layer. From this experiment, the particle size distribution usually in nano ranges from low to high ratio. The changes are noted by analytical instruments that also show the penetration of silver nanoparticles, making the steps easier to diffuse damaged skin (Hermans 2006).

4.1. Human skin permeation inductions using AgNPs

The procedure started with thick skin pieces collected by the surgical process as waste from the human abdominal region in which subcutaneous fat is taken out and hair shaved. Then, they are frozen at −25 °C for about four months, not longer than that for preservation; while freezing, there was no variation between the frozen cells and original cells, depending on the series another experiment is carried out. Also, the skin cell integrity of the sample was noted with the continuous-time interval of electrical conductivity by the use of a conductometer before and after the experiment with an operating range of about 300 Hz in which it is attached to a stainless-steel electrode.

4.2. Toxicity assessment of silver nanoparticles

The excessive level of silver nanoparticles accesses the toxic behaviours uptake by the organism; it is also responsible for the potentially toxic effects in both humans and animals. Therefore, the1se are tested mainly by medicinal applications such as ointments with effective antimicrobial combinations against various gram-negative, gram-positive bacteria, eukaryotic microorganisms, and other viruses. (Holmstrup 1991; Maynard et al., 2011).

Various silver mixed colloids are utilised for past experiments to treat the disease, and syndromes like tuberculosis, pneumonia, and syphilis etc., have been treated. But the studies which are conducted recently have displayed the presence and impact of silver particles leading to harmful effects *in-vivo* and *in-vitro* condition (Keiper 2007). Injection of silver ions and its exposure to the soft tissues layer cause argyria to the basal lamina in the skin (Miquel-Jeanjean et al., 2012; Morones et al., 2005; Okan et al., 2007). It is identified by the skin, which turns to bluish grey. Thus, this disease is clinically identified with the symptoms of excessive deposition of silver (Keiper 2007; Kollef et al., 2008) and by washing the nanoparticles, silver ions are gained. From unwashed silver nanoparticles are synthesised for NH_4OH catalysed the development of silver NPs in the surface of gold seed particles for toxicity assessment. Tangential flow filtration shows the concentration of the particles and utilises the extraction of unwashed and washed silver NPs depending on their extraction. From the filtration, the by-product uncleaned particles are produced and along with formaldehyde and methanol. The unwashed NPs been subjected to ultracentrifuge obtain toxicity testing.

Testing of two silver nanoparticles is carried out between unwashed and washed samples in *in-vivo* porcine skin. The few comparisons from 20 nm to 50 nm and its testing samples were often analysed to display oedema and HEK in reference to the Draize system. Aftermath the in-vivo test, the progression has been analysed under the macroscopic to differentiate the grey colour appearance to confirm the presence of silver nanoparticle on the surface of the skin. The best example of porcine skin to understand skin passage due to its thickness and absorption and mainly compared to the increase of silver nanoparticles in humans. Hence, it results in elongation and extension of epidermal hyperplasia, resulting in severe skin irritation.

5. Risk and health hazards

The interlinking of silver nanoparticles with the skin surface of humans contributes to the advantage and disadvantage, which are divided based on the exposure and penetration of nanomaterials in different medical tests. Therefore, these silver AgNPs have massive participation in the medical and health organisation. Furthermore, due to this property, silver does not show any harmful effects on humans; its application also increases in the medical field (Cummings et al., 2013).

Nanoparticles have a high chance of passing through the human system and easily interact with the cells, tissues and fluids present in the body. The nanoparticle that enters the body may cause some side effects such as immunological response and inflammation (FDA, 1999). Nowadays, utilising nano-based products and commercially derived nanoproducts such as clothes, cosmetics, medical, analytical products and surgical products have expressed their benefits to their consumer (Gratieri et al., 2010). However, prolonged exposure to that nanoparticle can cause some skin allergies, disorders, rashes and some other defects which have adverse effects on the brain cell (Kollef et al., 2008). Few *in-vivo* and *in-vitro* tests have shown adverse effects on human skin, all treated with medicinal products containing nanoparticles (Pal et al., 2007; Panyala et al., 2008). Silver nanoparticles are of great concern because of their effective antimicrobial activity against various diseases causing pathogens in the environment. Although however, the increased concentration of doped silver ion plays a vital role in eradicating the virulence properties of various microorganisms; they have a negative impact on the environment as well based because of their ability to cross-react with other chemical reagents/groups by physiochemical approaches (Sachdeva and Patolla, 2012).

5.1. Health risk

In everyday life, people are compelled to use nano-based products intentionally or unintentionally, which affects the different parts of the body. But there is no evidence to confer nanoparticles' role and their adverse effects on the human body during the exposure period (Buzea et al., 2007; Fung and Bowen, 1996). Although modern electronics, cosmetics, emulsions in paint, and other medical and non-medical equipment are also reported to have non-safety assessment with consumers due to their lower penetration rate and continuous exposure time (Chai et al., 2018).

Especially in medicine, incorporated devices and surgical masks that are impregnated medical equipment increase the risk of often exposure and continuous exposure of nanoparticles (Panyala et al., 2008). Several studies resulted in the *in-vivo* penetration of silver NPs with other metals like nickel, copper, metallic ions incorporation into the skin of humans. There is no study that states that skin lesion's adverse effects and absorption with the skin, which is damaged. A high range of absorption is shown in the metal powder and the cobalt and nickel powder (Hermans 2006).

The nanoparticles which are inflexible will pass through the skin quickly, and the less sized particles less than 30 nm can move quickly through the skin, and the dehydration is also high. This can also result in the easy pass-through of compounds and continuous exposure of silver nanoparticles specifically to the persons who work in the metal industries and in medical diagnostic centres, which allows contact-free permeation to the skin is also a reason. The micro AgNPs exposure in the human lung and the upper layer cells produces the reactive oxygen species (ROS), which generally leads to the damage of cells and stress, which shows adverse effects on health (Patlolla and Vobalaboina, 2008). In addition, some allergic reaction argyria zone heart valves are caused by silver nanoparticles, which is silver coated which protects the tissue growth also lesion effects (Labouta and Schneider, 2013; Lansdown, 2006).

6. Treatment and benefits of AgNPs

There are many commercial uses of silver nanoparticles; the silver-coated catheter is used to protect from many potential infections and prevent food poisoning (Patlolla et al., 2012; Pulit et al., 2011; Qin 2005; Rai et al. 2009). Nowadays, nanoparticles are used in cutting boards, tabletops, room spray, antibacterial in fabrics, and a disinfectant in the refrigerator (Kollef et al., 2008). The multiplication and the migration of infection can be prevented by this silver nanoparticle (Rai et al., 2009; Romoser et al., 2012; Saint et al., 1998). However, it has shown severe effects on animals that led to death. In such cases, various plant-mediated biological synthesis was tested to assess their efficacy against various pathogenic microorganisms to prevent diseases in the fishes and control the leaching of virulence factor (Thanigaivel et al., 2016; Thomas et al., 2014a,b).

The male reproductive system has shown adverse effects by the silver nanoparticles in which it causes sperm production effects and blood test barriers related to reproduction. In addition, this silver nanoparticle reacts with the protein content by binding; the relocation and the deposition led to direct contact with blood content which may later circulate throughout the body (Kulthong et al., 2010). It has also demonstrated a study that discusses the toxicity level of pristine- CNT nanomaterials and their exposure to the marine organism Donaxfaba, which is a bivalve organism used for the filter-feeding mechanism (Sekar et al., 2016). This was considered one of the best eco toxicity assessment studies to determine aquatic pollution (Saint et al., 2009).

Many ancient and modern therapeutic medicines are there which can treat all kinds of disorders through particle penetration. However, several nanoparticles, especially in silver nanoparticle, related to the disorder caused by AgNPs penetration and deposition, resulting in a condition called argyria; the protective method is developed using colloidal silver (Cowan et al., 2003; Lee et al., 2007). To detail the nanoparticle exposure inside the biological system, we have been reported specific vital nanomaterials. Their uptake mechanisms, such as magnesium oxide (MgO), plant oil-based nanoemulsions that exhibited a clear penetration route through gills and oral absorption of nanoparticles, leading to damage of internal organs that some extent it gives damages to the DNA and cause-specific chromosomal aberrations. This supported animal studies will be the best-case example to study the toxic exposure in various aquatic animals such as zebra fishes, giving the model of nanomaterials exposure upon human contact (Samberg et al., 2010; Schneider et al., 2009).

7. Conclusion

Silver nanoparticles or silver ion is a key particle and the placement of silver in nanotechnology mainly dependent on the bulk and ratio atoms. The silver nanoparticle potential of penetration depends on the size of the molecule. Comparing dimension range of the small molecular size is preferable for penetration of the skin. The permeation of the silver nanoparticles through the dermal tissue or skin is carried out through continuous delivery. The release of AgNP on the layer and the limit of permeation are also based on the skin layers distance and thickness in hair follicles in the outer layer. Most common applications of AgNP in the field of catalysis, electronics and optics due to its properties like the magnetic, electrical and compact size the usage of these nanoparticles is vast in the application. In textile engineering, bioengineering, and water treatment are the biotechnological fields where silver-based nanoparticles are used and nano silver-based consumer products. The bone cement, surgical instrument, surgical mask and wound dressing are also made with these silver nanoparticles. These are the mandatory interference of silver nanoparticles and their impact; it also has some hazardous effect when the amount crosses the limit.

8. Future prospects

In future, the research on silver nanoparticles is to combine different functions into multifunctional nanoparticles. For a sample, the semi-metallic or the metallic particles combined are the reason for the production of potential energy that is comfortably fit for transporting medium and the production of different biomaterials. The proposed method is highly useful in the drug delivery system, which has played an essential role in releasing the biomolecular to a targeted site. The exciting and unique technique of image contrast agent is to detect or accumulate nanoparticles scattered throughout the body (Kulthong et al., 2010; Shinde et al., 2014). Such uncontrolled leaching and environmental exposures of Nano silver in the environment can be controlled by natural remediation or biological remediation (Simko et al., 2010; Tiwari and Nanda, 2013; Toedt et al., 2005).

Data availability statement information

Data sharing does not apply to this article as no new data were created or analysed in this study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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