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Review

Evaluation of silver nanoparticles in cosmeceutical and potential biosafety complications



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ABSTRACT

Silver nanoparticles are well received in the cosmeceutical industry due to their broad spectrum of pharmacology applications. Research on the therapeutic properties exhibited by silver nanoparticles revealed that the antimicrobial and anti-inflammatory properties are the main attraction in the establishment of nanocosmeceutical products whereby their mechanisms of action are reviewed in this paper. In addition, studies on other uses of silver nanoparticles acknowledged that the particles act as antifungal agents in nail polishes and pigments in coloured beauty products such as lipsticks and eye shadows. Despite the extensive use of silver nanoparticles in the cosmetic line, there are still limited resources on the mechanism of actions and the effect of the particles on the bio-functionality of the body. The safety of silver nanoparticles could be comprehended from their skin penetration ability and toxicity to the human body in which it could be justified that both features are mainly influenced by the morphology of the particles and the method of application. This article summarizes exclusively on the synthesis of silver nanoparticles, the biomedical mechanisms and applications as well the limitations with respect to skin penetration ability and toxicity effects which will contribute significantly to the vast research on the association of nanotechnology and cosmetics.

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1. Introduction

With the growing demand of skincare and beauty products in the market, the cosmetic industry has expanded exponentially over the years. However, the current demand has diverted towards products that improve overall skin quality. Consumers have been showing interest in products that provide long-term effects and numerous benefits to the skin. Hence, the invention of the term 'cosmeceutical' which implies the overlapping of pharmaceuticals and cosmetics (Cavinato, 2019). A cosmeceutical product is said to contain biologically active ingredients that not only treat skin problems but also preserve skin health (Draelos, 2019). The global cosmeceuticals market has garnered about USD 46.93 billion in 2017, with a forecast of USD 80.36 billion by 2023, registering a compound annual growth rate (CAGR) of 9.38% from 2016 to 2022. Evidently, consumers are willing to pay a higher price for products that enhance their skin functionality and thus encourage cosmetic manufacturers to develop and offer more variety of these products (Draelos, 2014).

Nanotechnology has been introduced in the cosmeceutical market in the early 1980 s, with reference to the term 'nanocosmeceutical'. As the competition in the cosmeceutical market continue to grow immensely, new cosmetic formulations have emerged and manufacturers are constantly improvising to deliver products with higher efficacy. The cosmetic field is one of the early adopters of nanotechnology as its role significantly contributes to superior cosmetic effects from improved skin penetration and stability as well as effective release of ingredients through the skin barrier. Nanotechnology is widely incorporated in the production of various cosmeceutical line such as sunscreens, nail care, lip care, face cleansers, hair repair shampoos, moisturizing and whitening creams as well as anti-aging products (Lohani et al., 2014). The two common types of engineered nanomaterials are titanium oxide and zinc oxide. However, other nanosized materials such as gold and silver metals, metal oxides, liposomes, nanocapsules, cubosomes, dendrimers, niosomes, nanocrystals and solid lipid nanoparticles have begun to be used in cosmetic applications (Cao et al., 2016).

Silver nanoparticles (AgNPs) are one of the most widely researched metallic nanoparticles as they are industrialized for multiple purposes. As stated by Pirtarighat et al. (2019), the strong inhibitory effect of AgNPs on a large spectrum of microbial species is one of their most highly regarded property. As a result, AgNPs received much attention not just in the pharmaceutical industry

as a potential substitute for antibiotics but also in the textile industry particularly water filtration (Haider and Kang, 2015; Pirtarighat et al., 2019). Furthermore, AgNPs possess impressive anti-inflammatory effect which is vital in wound healing and medical applications. With those critically acclaimed therapeutic effects, AgNPs are exploited for the formulation of skin cleansers, lotions, creams, deodorants, shampoos and toothpastes (seen in Table 1) (Gajbhiye and Sakharwade, 2016). Besides its antimicrobial and anti-inflammatory effect, AgNPs are proven to have anti-cancer properties as reported on human cell lines as well as animal models whereby AgNPs could inhibit cancer cell growth and induce apoptosis (Jeong et al., 2016; Yang et al., 2016).

The application of nanocosmeceutical has soared rapidly yet there are limited research available regarding the mechanism of action of AgNPs and the safety aspects. Therefore in this review, the main features of AgNPs are highlighted and their respective means of interaction to produce pharmaceutical effect leading to their impeccable roles in the cosmeceutical field are elucidated comprehensively. The controversial element of AgNPs which is their toxicity towards the biological functions of humans or animals were also deeply considered and outlined in this paper.

2. Synthesis of silver nanoparticles

2.1. Chemical-reduction synthesis

Just like every other nanoparticles, AgNPs are synthesised via several different means (Fig. 1) with chemical reduction method as one of them. Chemical synthesis of AgNPs comprised of the reduction of silver ions (Ag^+) in aqueous or non-aqueous solutions into metallic silver by organic or inorganic reducing agents in the presence of hydroxyl groups (Siegel et al., 2012). Evidently, chemical synthesis requires three fundamentals; Ag precursors, reducing agents and stabilizing agents. Sodium citrate, ascorbate, sodium borohydride ($NaBH_4$), elemental hydrogen, Tollens reagent, N, N-dimethylformamide (DMF) and glucose are examples of reducing agents used in this procedure (Irvani, 2014). Although there are other techniques recommended for chemical synthesis of AgNPs such as polyol method (Tarek and El-Aziz, 2019) and radiolytic process (Uttayarat et al., 2015), chemical reduction is the preferred method as it promotes high yield with less cost and prevents aggregation of the particles formed (Gudikandula and Maringanti, 2016). The process and nature of reducing agents in the synthesis of AgNPs can significantly affect the size and shape

Table 1
Patent review on the incorporation of silver nanoparticles in cosmeceutical products.

Title	Publication number	Publication date	Applicant
Cosmetic pigment composition containing gold or silver nano-particles	WO2007011103A1	2007-01-25	Korea Research Institute of Bioscience and Biotechnology
Skin lotion comprising aqueous dispersion of ultra-fine noble metal particles	HU0401663A2	2005-09-28	Phild Co., Ltd.
Anti-microbial body care product	US20020122832A1	2002-09-05	Bernhard Hanke
Method for treating human keratin fibers with organomodified metallic particles	US7186274B2	2007-03-06	L'oreal
Formulations including silver nanoparticles and methods of using the same	WO2015057983A1	2015-04-23	University of South Alabama
Colored nanoparticles for cosmetic and its manufacturing method	JP2009221140A	2009-10-01	National Institute Of Advanced Industrial & Technology
Colloidal silver, honey, and helichrysum oil antiseptic composition and method of application	US5785972A	1998-07-28	Tyler; Kathleen A
Toothpaste or tooth gel containing silver nano particles coated with silver oxide	US20130017236A1	2013-01-17	Robert Johnson Holladay

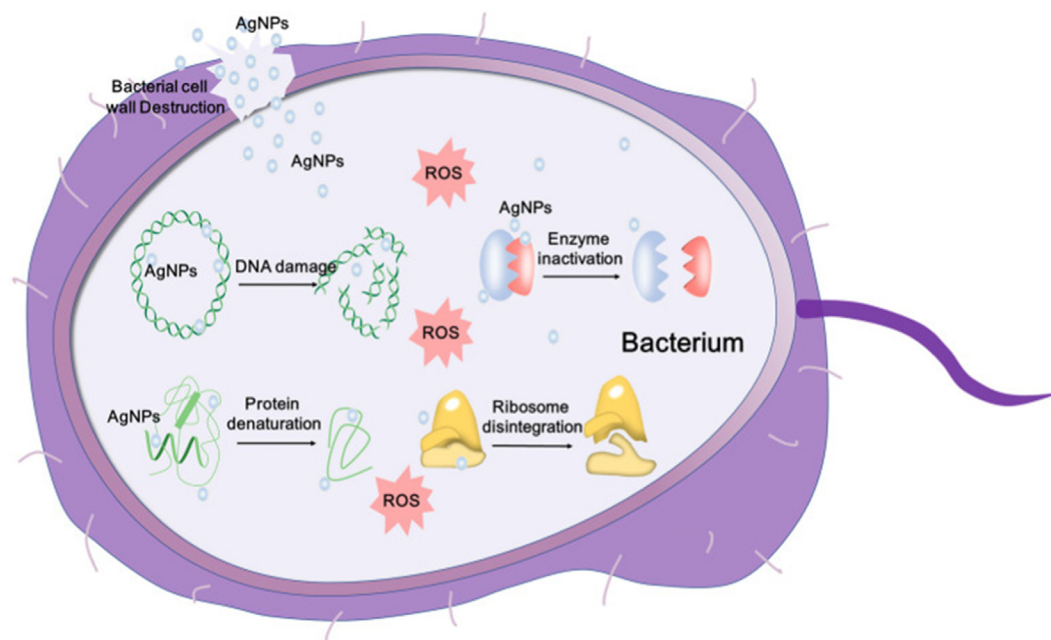


Fig. 1. Schematic representation of the mechanisms of AgNPs against bacteria, depicting ROS-dependent pathway, DNA damage, protein denaturation and enzyme inactivation for antibacterial action of AgNPs from Xu et al. (2020) under the terms of the Creative Commons CC BY License, <https://creativecommons.org/licenses/by/4.0/>

of the particles and therefore altering the chemical and physical properties of the particles. The reactivity of the reducing agent to the redox potential of the metal should be adjusted during the process in order to control the reaction rate. If the reaction rate is accelerated with high speed, the particles formed will be too small due to excessive production of vast amount of metal nuclei. Meanwhile, if the reaction rate is too low, agglomeration of the particles will occur (Suriati et al., 2014).

2.2. Physical synthesis

Besides chemical synthesis, physical method is another alternative adopted by researchers. Among the preminent physical methods involved in the synthesis of AgNPs are the use of laser ablation, evaporation–condensation and ultraviolet (UV) radiation. However, most of the physical methods are not only time consuming but also require high energy and thus most costly. For instance, a large space is needed for the tube-furnace evaporation–condensation method along with the usage of high energy, heat released to its surroundings and a long time to achieve thermal stability. With that being said, more substitutes have been developed in order to counteract those complications. To illustrate, Jung et al. (2006) attempted the synthesis in a small ceramic heater where nanoparticles are formed through nucleation and growth. In this method, surface temperature achieved thermal stability in a shorter time and maintained uniformly leading to production of small particles in high concentration. Another improved method that had been explored is the thermal decomposition whereby monodispersed silver nanocrystallite were formed from reaction of silver nitrate (AgNO_3) with sodium oleate at elevated temperature of 290 °C (Lee and Kang, 2004). The uniformity of size and shape of AgNPs are mostly determined by the thermal, ac power and arc discharge that are employed in physical synthesis (Haider and Kang, 2015).

2.3. Bio-synthesis

Nevertheless, the chemical synthesis of AgNPs involves chemical compounds such as sodium borohydride and hydrazine that

may adhere to the surface of the particles and could contribute harmful effects contained in the end product (Rauwel et al. 2015). Furthermore, the conventional way of synthesizing AgNPs are costly and requires high energy expenditure as heat treatment is also involved (Ahmed et al., 2016). With the current trend of ‘going green’, researchers have been exploring a more cost-effective and environmental-friendly way of producing nanoparticles. Hence, assorted biological resources such as plants and microbes (yeast, fungi and bacteria) are used in the green synthesis of silver nanoparticles. The presence of biomolecules such as amino acids, proteins, vitamins, enzymes and polysaccharides as well as secondary metabolites in the extracts of these sources contribute to the reduction reaction in the process (Keat et al., 2015; Siddiqi et al., 2018). For instance, Sahoo et al. (2020) had utilized cyanobacterium *Chroococcus minutus* as a biological reducing agent to synthesize AgNPs as novel antibacterial agents against upper respiratory tract infection. In addition, cubical, spherical and truncated triangular shaped silver nanoparticles with average size of 88.87 nm were synthesized by green algae (*Botryococcus braunii*) in another experimental study (Arya et al., 2019). An endangered medicinal plant known as *Withania coagulans* was used as in the formation of AgNPs with average size 14 nm and spherical in shape. Results had shown that these particles were capable of exerting antioxidant and antibacterial effect on tested microorganisms (Tripathi et al., 2019).

3. Roles of silver nanoparticles in cosmetic products

3.1. Antibacterial

One of the exceptional abilities of AgNPs is their strong antibacterial property. Researchers utilize this property by incorporating AgNPs as active ingredients in the preparation of skincare products, toothpastes and deodorants [Raj et al., 2012; Effiong et al., 2020]. As shown in Fig. 1, AgNPs have the ability to exercise antibacterial features via several mechanisms. According to Dos Santos et al. (2014), AgNPs exert antimicrobial activities through

the mechanism of a bactericidal whereby AgNPs adhere to the cell wall and react with the membrane proteins. This is further supported by Qing et al. (2018) whom stated that the adhesion allows AgNPs to infiltrate and damage the cell membrane, leading to leakage of cellular contents. Structural damage of bacteria caused by AgNPs were observed by Huq et al. (2020). In their study, morphological changes could be seen on *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) that were treated with AgNPs in which both cells had distorted and deformed inner and outer surfaces (Huq, 2020). Furthermore, in the cell, the silver ions (Ag^+) are released to attack the respiratory chain and causing oxidative stress with an increase in production of reactive oxygen species (ROS). This ultimately leads to protein damage and inhibition of cell growth. This can be evidently proven from a study conducted by Yan et al. 2018 on *P. aeruginosa* (Yan et al., 2018). As a result, cell growth is disrupted and eventually leads to cell necrosis. Besides the respiratory chain, research have stated that AgNPs also attack the DNA mechanism in the cells. According to a study, microscopic analysis of *Escherichia coli* (*E. coli*) and *S. aureus* revealed that the DNA of the bacteria cells had shrunk and condensed after treatment with AgNPs (Chatterjee et al., 2015). Likewise, Widdatallah et al. (2020) manifested the inhibition of *E. coli* and *S. aureus* by AgNPs synthesised by *Nigella sativa* seeds (Widdatallah et al., 2020). AgNPs hinder the transcription and translation process by attaching to the phosphorus and sulphur groups of the nucleotide bases and induce the unwinding of DNA (Prabhu and Poulouse, 2012; Liao et al, 2019). Alteration of the DNA leads to interference of the replication process as well as gene expression of essential proteins and enzymes. Consequently, the deactivation of respiratory enzyme by AgNPs at the cytoplasmic membrane will essentially interrupt the production of adenosine triphosphates (ATPs) [36]. Additionally, cell enzymatic function can be inactivated via the interaction between AgNPs and released Ag^+ with the thiol and sulphhydryl groups of the enzymes respectively (Prabhu and Poulouse, 2012).

The effectivity and efficiency of this particular property are shape and size dependent. Several studies have been conducted to prove the effect of the shape and size of AgNPs on the antibacterial activity as displayed in Table 2. Based on the studies conducted, it could be deduced that smaller-sized AgNPs had higher effectivity in microbial inhibition. This is due to the large surface to volume ratio that enable the AgNPs to penetrate through the membrane more efficiently and actively disrupt the structure as well as the cell metabolism in the bacteria (Duran et al., 2010). Another factor to be considered that is the shape of the nanoparticles. For instance, Pal et al. 2007 evaluated the bactericidal action

of truncated triangular, spherical and rod-shaped AgNPs on gram-negative bacterium *E. coli*. From their observations, it could be deduced that truncated triangular-shaped AgNPs performed better antibacterial activity compared to the other two shapes. AgNPs with the same size or surface areas could also exert different antibacterial capacity due to the difference in shape as the effective surface areas and active facets of the AgNPs may vary (Dakal et al., 2016). Table 3.

This property of AgNPs is deeply acknowledged in the cosmetic industry and therefore they are used as preservatives in various cosmetic line in order to prevent growth of pathogenic microorganism which could affect the quality of the products and human health as well as the integrity of the brand. On top of that, this elemental feature enables AgNPs to be implemented as a treatment for bacterial-induced skin complications such as acne in the form of cream or gel. Some skin cleansers and body soaps also contain AgNPs and are used for acne prone skin or sun-damaged skin. An example of these cleansers are the nanocleanser pink soap produced by Nano Cyclic Inc. that helps to reduce age spots, bacteria and fungi colonization as well as to treat acne (Nafisi and Maibach, 2017). AgNPs are also used in combination with fluoride in toothpaste to prevent formation of carries and promote self-cleaning against plaques (García-Contreras et al., 2011). In a patent review, AgNPs are added into toothpaste or oral care gels at a concentration between 0.0005% and 0.004% as to inhibit bacteria growth that leads to unpleasant oral smells and dental cavities (Holladay, 2011). Silver nanoparticles (AgNPs) are incorporated in anti-dandruff shampoos in order to prevent the buildup of *Malassezia* species responsible for the itching and scaling of the scalp (Sathishkumar et al., 2016).

3.2. Anti-inflammatory

Other than the ability to inhibit microbial growth, the role of AgNPs in the wound healing process has become a crucial area in therapeutic research and modern medical practice. Agarwal et al. (2019) disclosed that AgNPs substantially disrupt the Vascular Endothelial Growth Factor (VEGF) pathway which is responsible for the T-helper type-2 (TH2) cell-mediated inflammation promoted by secretion of pro-inflammatory cytokines like IL-4, IL-5, IL-9 and IL-13.

Several literature evidence based on animal studies reported that AgNPs alter the inflammatory response via various mechanisms. For instance, one of them suggested that AgNPs lower wound inflammation and regulate the release of fibrogenic cytokines in a thermal injury animal model thus promoting rapid heal-

Table 2
Studies on the effect of size and shape of AgNPs on the antimicrobial activity.

Journal	Size	Shape	Antimicrobial activity
Jeong et al., 2014; Dong et al., 2019; Helmlinger et al., 2014; Martinez-Castanon et al., 2008; Osonga et al., 2020	10 nm and 100 nm 10 nm, 30 nm, 60 nm and 90 nm 40–80 and 120–180 nm, 20–60 nm, 140–180 nm, 80–120 nm 7 and 29 nm, 89 nm 9, 16, 30, 35 nm and 21, 27 nm	Spherical Spherical Spherical Platelets Cubes Rods Spherical Pseudospherical Spherical Quasi-spherical	10 nm nanoparticles showed more antimicrobial activity than 100 nm particles on <i>Methylobacterium spp.</i> Both MIC and MBC values for 10 nm size AgNPs were the lowest while 90 nm sized AgNPs had the highest values. Silver nanoplatelets showed the highest antibacterial effect on <i>S. aureus</i> , followed by spheres, rods, and then cubes 7-nm silver nanoparticles present the best antibacterial against <i>E. coli</i> and <i>S. aureus</i> . 7 nm silver nanoparticles showed the highest antibacterial effect against <i>E. coli</i> and <i>S. aureus</i> . Smaller sized spherical (9 nm) and quasi-spherical (21 nm) AgNPs exhibited highest inhibition on tested fungi (<i>Aspergillus nidulans</i> , <i>Trichaptum biforme</i> , <i>Penicillium italicum</i> , <i>Fusarium oxysporum</i> , and <i>Colletotrichum gloeosporioides</i>) and bacteria (<i>Pseudomonas aeruginosa</i> , <i>Aeromonas hydrophila</i> , <i>Escherichia coli</i> , <i>Citrobacter freundii</i> , <i>Listeria monocytogenes</i> and <i>Staphylococcus epidermidis</i>)

Table 3
Effect of synthesis on the size and shape of AgNPs.

Types of synthesis		Physical properties of AgNPs (size, shape)	Source
Physical	a) Laser ablation in – ethylene glycol – distilled water – chitosan – aqueous monomers isobutyl acrylate	Average size of 22.08 nm, spherical shaped Average size of 27.41 nm, spherical shaped Average size of 10.50 nm, spherical shaped	Tajdidzadeh et al., 2014Tajdidzadeh et al., 2014Tajdidzadeh et al., 2014 Christopher et al., 2011Raffi et al., 2007
	b) Inert gas condensation using helium	Size < 25 nm, spherical shaped Size range from 9 to 32 nm, spherical shaped	
Chemical reduction	a) 3-hydrazino-isatin	Size range 18–21 nm, monodispersed spheres	El-Faham et al., 2014El-Faham et al., 2014Guzman et al., 2008Szczezanowicz et al., 2010Khatoon et al., 2011Suriati et al., 2014
	b) 1-benzyl-3-hydrazino-isatin	Size range of 17–20 nm, monodispersed spheres	
	c) Hydrazine hydrate	Size range 8–50 nm, agglomerates of small grains	
	d) Sodium borohydride	Size < 20 nm, small spherical shaped grains	
	e) Trisodium citrate	Size range of 100–200 nm, agglomerates of small grains Size range of 35–80 nm, quasi spherical/polygonal	
Green/Bio- synthesis	a) Plants – <i>Cissus rotundifolia</i> leaf extract	Size range of 20–40 nm, spherical and oval-shaped	Al-Ghamdi, 2018Qais et al., 2019Erdogan et al., 2019Behravan et al., 2019Ahmed et al., 2016Bindhu and Umadevi, 2013Masum et al., 2019Singh et al., 2015Huq, 2020Deljou and Goudarzi, 2016Niknejad et al., 2015AbdelRahim et al., 2017Saravanan et al., 2017
	– <i>Murraya koenigii</i> (curry leaves extract)	Size range of 5–20 nm, spheroidal shaped	
	– <i>Cynara scolymus</i> leaf extract	Diameter range of 200–223 nm, spherical shaped	
	– <i>Berberis vulgaris</i> leaf and root extract	Size range of 30–70 nm, spherical shaped	
	– <i>Azadirachta indica</i> leaf extract	Average diameter around 34 nm, spherical shaped	
	– <i>Hibiscus cannabinus</i> leaf extract	Average size of 9 nm, monodispersed spheres	
	– <i>Phyllanthus emblica</i> fruit extract	Size range of 19.8–92.8 nm, spherical shaped	
	b) Microbes – <i>Brevibacterium frigoritolerans</i> DC2	Size range of 10–30 nm, spherical shaped	
	– <i>Pseudoduganella eburnea</i> MAHUQ-39 (soil)	Size range of 8–24 nm, spherical shaped	
	– thermophilic <i>Bacillus</i> Sp. AZ1 (hot spring)	Size range of 7–31 nm, single/ aggregated spherical shaped granules	
	– <i>Saccharomyces cerevisiae</i> (yeast)	Size range of 5–20 nm, small and spherical shaped	
	– <i>Rhizopus stolonifer</i> (black bread mold)	Average size of 9.46 ± 2.64 nm, spherical shaped	
	c) Exopolysaccharide (EPS) from <i>Leuconostoc lactis</i>	Size range of 30–200 nm, spherical shaped	

ing. Additionally, a decrease in inflammation markers such tumor necrosis factor- α (TNF- α) and interleukin (IL)-6 was observed in animals treated with AgNPs (Wong et al., 2009; Seung et al., 2018). The ability of green-synthesised AgNPs by *Prunus serrulate* fruit extract to reduce the expression levels of other inflammatory mediators such as nitric oxide, prostaglandin E₂ and inducible nitric oxide synthase in lipopolysaccharide (LPS)-induced RAW264.7 cells, derived from murine macrophage cells was demonstrated by Singh et al. (2017). Apart from these mediators, the study revealed that AgNPs exerted inhibitory influence on NF- κ B (Nuclear Factor- κ B) signalling which is responsible for various inflammatory diseases via p38 MAPK (Mitogen-activated protein kinase) pathway. The potentiality of AgNPs as anti-inflammatory agents had been proven from another animal study on the healing process of anastomosed intestinal tissue of mice using AgNP-coated suture. Macroscopic observation showed a more effective and long-term tissue healing process with a resemblance of a normal intestinal tissue along with reduced inflammatory response using the AgNP-coated suture compared to the control and antibiotic-suture groups (Liu et al., 2017). Quantitative evaluation displayed less macrophage infiltration and reduced expression levels of proinflammatory cytokines even when the tissue healing process reached the later stage. Inhibition of enzyme cyclooxygenase which then suppresses prostaglandin (PG) synthesis in the inflammatory response was demonstrated by bio-synthesised AgNPs on carrageenan-induced hind paw oedema model in rats (El-Rafie and Hamed, 2014).

Human cell lines have also been used extensively to determine the role of AgNPs in the inflammatory response system. For instance, Aparna Mani et al. (2015) had found that AgNPs synthesised by *Piper Nigrum* extract were able to reduce the expression levels of TNF- α , IL-1 β and IL-6 in human PBMC cells. In another study, it was concluded that AgNPs were able to downregulate the production of a vital proinflammatory mediator known as cyclooxygenase-2 (COX-2) in normal human dermal fibroblasts (NHDFs) and normal human epidermal keratinocytes (NHEKs) (Frankova et al., 2016). Moreover, the anti-inflammatory effect of AgNPs could be observed in tumor necrosis factor- α (TNF α)-induced inflammatory response in human pulmonary epithelial cell line (NCI-H292) in a dose-dependent manner. Gene expression levels of TNF α -induced IL-1 β and IL-18 were significantly reduced due to exposure of AgNPs with concentrations of 10 and 100 μ g/ml as reported in the study by Fehaid et al. (2020).

The ability of AgNPs to act as a new source of anti-inflammatory drug is essential in the manufacturing of skin ointments and creams. With the combination of both antibacterial and anti-inflammatory property, AgNPs can be a potential active ingredient in the formulation of skin care products used to treat acne. They can perform by minimizing not only the growth of *Propionibacterium acnes* (*P.acnes*) and other bacteria but also the inflammation induced by *P.acnes* (Prabhu and Poulouse, 2012; Patil and Muthusamy, 2020). Such impressive characteristic possessed by AgNPs was tested on patients with psoriasis vulgaris and was proved that to be more effective than hydrocortisone (David et al., 2014). In accordance to that, greater amount of studies have been conducted to demonstrate that AgNPs are capable of treating wounds, cuts and burns. In relation to that matter, treatment for ultraviolet (UV) radiation-induced damaged skin with the application of AgNPs in the formulation of various compositions such as sunscreens, sunburn relief formulations, hand, body and/or facial moisturizers, topical analgesic have been patented due to their healing properties and anti-inflammatory effect (Singh et al., 2005).

3.3. Other roles of silver nanoparticles in cosmetic

One of the new strategies which may have great potential in the cosmeceuticals is the incorporation of nanoparticles having anti-fungal activity (silver and metal oxide nanoparticles) in nail polish to treat fungal toenail infections (Lohani et al., 2014). The use of nanoparticles like silver as cosmetic pigment has been patented whereby it is stated that AgNPs in combination of gold nanoparticles provide yellow–red pigment in the manufacturing of diverse cosmetic products such as foundations, eye shadows, powders, lipsticks, inks, varnishes or eyebrow pencils (Ha et al., 2005; Pulit-Prociak and Banach, 2016).

3.4. Skin penetration of silver nanoparticles

Skin serves as the main exposure to nanoparticles especially when incorporated into topical applications in cosmetic products. However, the skin itself act as a barrier against foreign objects through its layers known as the stratum corneum (the horny layer), the dermis and the subcutaneous wherein the stratum corneum has the highest barrier function. Theoretically, the smaller the size of the particles, the higher the rate of penetration (Yokota and Kyotani, 2018). Cardoso et al. (2017) demonstrated that a higher amount of smaller sized AgNPs were able to penetrate through the skin on the back of a pig's ear as compared to silver nitrate (AgNO₃) due to its larger size. Another reported factor on the penetration ability of AgNPs is the condition of the skin (Staron et al., 2020). Larese et al. (2007) had conducted an *in vitro* study regarding the penetration of AgNPs (25 nm) on damaged and intact skin whereby they verified that AgNPs absorbed through the intact skin was low but detectable (0.46 ng/cm²) whereas there was an increase in amount of AgNPs penetrated through the damaged skin (2.32 ng/cm²). On the contrary, several papers have also disclosed that AgNPs were able to be absorbed through the skin and precipitated at the stratum corneum. The authors also reported the presence of aggregates of the particles at stratum corneum which could potentially prevent further penetration into deeper layers (Bianco et al., 2016; Wang et al., 2016). However, an *in vivo* analysis had been carried out on 16 healthy with normal intact skin and it had been observed that AgNPs were able to penetrate deeper than stratum corneum and into the reticular dermis (George et al., 2014). Nonetheless, none were found in the systemic circulation.

Some researchers had also concluded in past studies that the skin penetration of AgNPs could be shape-dependent. According to a study by Tak et al. (2015) on the skin permeability of the spherical silver nanoparticles (SNPs), rod-shaped silver nanoparticles (RNPs) and triangular silver nanoparticles (TNPs), it was found that RNPs had the highest penetration capability whereas TNPs recorded the lowest penetration capability. From Table 2, it could be justified that the method of synthesis of AgNPs and the reduction agents used contribute to the variety of sizes and shapes of the particles. Along with size and shape of the nanoparticles, the surface properties (polarity/charge), the formulation of the particles (hydrophobicity) and the application method can affect the penetration behaviour of a AgNPs (Liang et al., 2013). In another context, Bianco et al. (2014) documented an experiment on the permeation of AgNPs on three human skin graft samples (fresh, cryopreserved and glycerol-preserved) that are most commonly used in burns recovery, all of which has decreasing cell viability. From the results obtained, it could be observed that more AgNPs could penetrate through glycerol-preserved skin (non-viable cells) compared to fresh and cryopreserved (64% viability) skin samples. Nonetheless, the difference in the amount of AgNPs found in both fresh and cryopreserved skin were insignificant and thus indicating that cell viability is not a factor in the percutaneous absorption of

AgNPs and suggesting that the absorption occurs through passive diffusion (Chen et al., 2013).

3.5. Cellular and toxicity effects of silver nanoparticles

As the exploitation of AgNPs continue to magnify due to their intrinsic biomedical applications, their toxicity effects on human health as displayed in Fig. 2 has become a more apparent concern with the number of studies conducted progressively by researchers to explore this grey area. While it is known that AgNPs has cytotoxic effect on different bacteria species and viruses such as HIV-1 and canine distemper virus (CDV), many *in vivo* and *in vitro* studies were performed on various animal models and human cell lines to determine the adverse effects of AgNPs on normal and cancer cells (Chen et al., 2013; Bogdanchikova et al., 2016). Some studies illustrated different toxicity effect of AgNPs at various concentrations. For instance, Kokura et al. (2010) stated that AgNPs at concentration of 0.002–0.02 ppm had no effect on human keratinocytes or UVB-induced cell death. Meanwhile, another recent analysis done by Vazquez-Munoz et al. (2017) showed that at cellular level, the toxicity effect of AgNPs was similar for all biological systems tested; Rift Valley Fever Virus (RVFV), bacteria (*Staphylococcus aureus* and *Escherichia coli*), microalgae, *Candida albicans* (yeast), *Fusarium oxysporum* (filamentous), mammalian cell lines (Vero and Murine Antigen-presenting Dendritic Cells) and human cancer cell lines (HeLa and MDA-MB-231) whereby the inhibitory concentration range was 10 µg/mL.

Several genotoxicity studies have also been run by researchers on human and animal cell lines to further elaborate of the mechanism of AgNPs. DNA damage in the form of DNA strand breaks in mouse lymphoma cells and HK-2 immortalized human proximal tubule cells were most evident when incubated with AgNPs compared to several other nanomaterials (Mei et al., 2012; Kermanizadeh et al., 2013). Oxidative DNA damage by AgNPs was also imposed on three human cells, human colorectal adenocarcinoma (HT-29), human epithelial cell line (A549) and human

hepatic cell line (HepG2) as reported by Kruszewski et al. (2013). Haase et al. (2012) analyzed the effects of AgNPs on primary neural cells from Wistar rats and found that AgNPs induced the production of ROS along with acute calcium dysregulation. This justified that prolonged exposure to AgNPs may disrupt the central nervous system. This finding is further supported by a later study whereby it was proven that AgNPs induced inflammatory response on mouse neuron cells and deposition of amyloid-β (Aβ) plaques which is a cause of neurodegenerative disorder, Alzheimer's disease (AD) (Huang et al., 2015). A comparative study between the cytotoxic effect of AgNPs on normal and cancer cells were conducted by AshaRani et al. (2008). Exposure to AgNPs led to formation of ROS, reduction of ATP content and DNA damage on both normal human lung fibroblast cells (IMR-90) and human glioblastoma cells (U251). Therefore, it is evident that AgNPs posed cytotoxicity and genotoxicity effect not only on unhealthy, cancerous cells but also on normal cells.

The toxicity effect of AgNPs are determined and influenced by multiple factors hence the inconsistent data reported. According to literature, the cytotoxicity effect of AgNPs are associated with the release of silver ions from the surface whereby human cell lines showed a much greater vulnerability towards silver salts as compared to AgNPs (Koch et al., 2012; Barbasz et al., 2017). Additionally, the size and morphology of the nanoparticles can strongly affect the mode of actions of the AgNPs. Size-dependent toxicity effect of AgNPs was proven in a study whereby 10 nm of particles portrayed significantly greater toxicity compared to 50 nm, 100 nm and 200 nm particles (Wildt et al., 2016). Similarly, Williams et al. (2016) observed most significant effect on human T84 epithelial cells by 10 nm AgNPs compared to 20 nm, 75 nm and 110 nm. In a review, it was stated that the surface charge developed by surface functionalization can significantly affect the toxicity of mechanism of AgNPs in which their uptake into cells are determined by the magnitude of surface charge measured as zeta potential (Burdusel et al., 2018). Meanwhile, the shape-dependent toxicity of AgNPs was illustrated in a comparative study

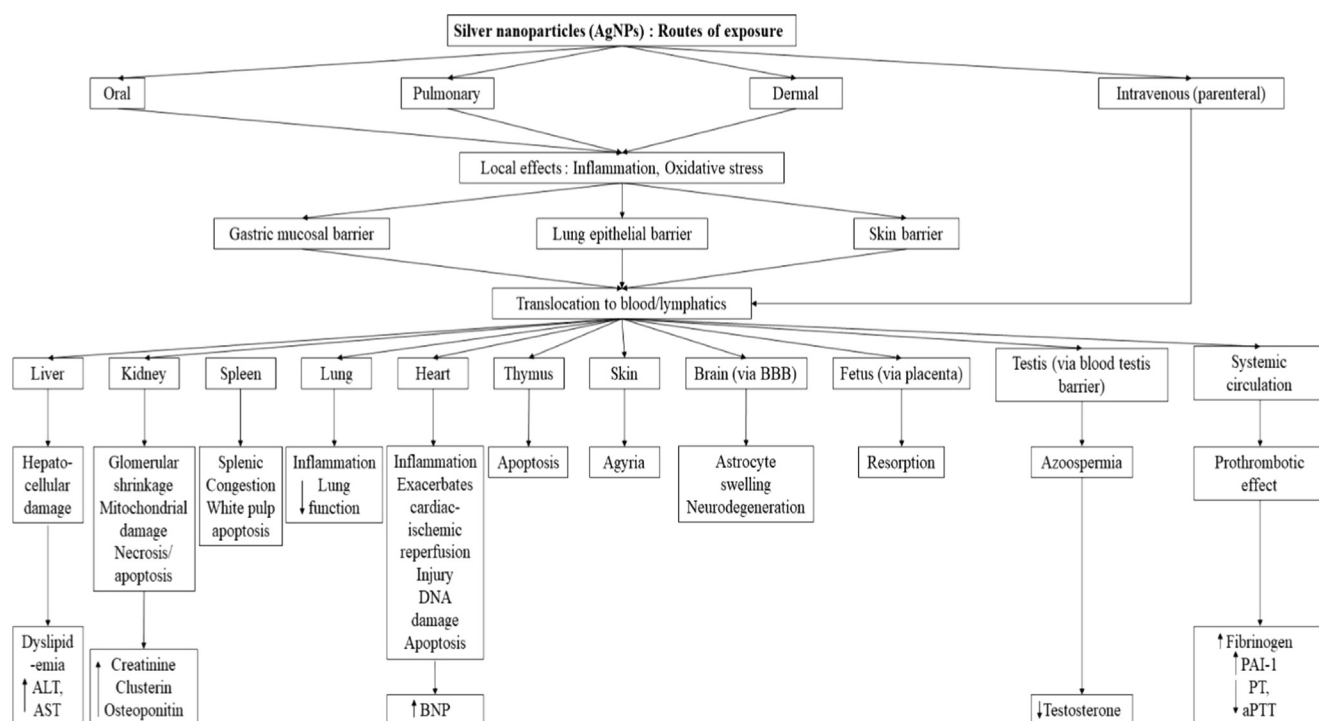


Fig. 2. Schematic representation of the biodistribution and toxicity of silver nanoparticles (AgNPs) following various routes of exposure from Ferdous and Nemmar (2020) under the terms of the Creative Commons CC BY License, <https://creativecommons.org/licenses/by/4.0/>

on the effect of silver wires (diameter 100–160 nm), spherical silver nanoparticles (30 nm) and silver microparticles (<45 µm) synthesized by wet chemical methods on human alveolar epithelial cells (A549). Based on the results reported, reduction of cell viability and increased lactic acid dehydrogenase (LDH) release by silver wires were observed while spherical AgNPs showed no such effects (Stoehr et al., 2011). The physicochemical properties of AgNPs such as their chemical nature, reactivity, composition as well as the presence of aggregation are other factors affecting the toxicity of the particles that should be considered (Korani et al., 2015). Galandakova et al. (2016) had claimed that ionic silver was more cytotoxic compared to AgNPs on NHDF and NHEK. Based on their study, the authors have concluded that the concentration of AgNPs that is suitable to be included in wound healing formulation was till 25 µg/mL.

Put simply, it is established that AgNPs are able to exert toxicity by inducing apoptosis, increasing the production of reactive oxygen species (ROS) leading to oxidative stress and causing DNA damage on a broad spectrum of bacteria species, viruses as well as human cancer cell lines (Dos Santos et al., 2014; Kora and Sashidhar, 2018). These beneficial effects encourage AgNPs to be explored and used extensively as a novel material in the modern therapeutic applications and devices. However, it is not entirely coherent on whether AgNPs exert similar effects on cellular membrane and organelles such as the nucleus, mitochondria, and lysosomes on normal human cell lines which could potentially lead to the disruption of human biofunctionality.

4. Conclusion

To summarise the above, silver nanoparticles (AgNPs) are undoubtedly critical and valuable addition to the cosmeceutical industry due to their advantageous, therapeutic attributes. With that said, AgNPs contribute enormously to the emergence of new and diverse formulations in the cosmetic line that could prevent or treat prevalent skin diseases, heal damaged skin and subsequently preserve overall skin health and quality for long-term.

The efficiency of these nanoparticles to deliver their beneficial effects are influenced by their physical and chemical properties which in turn, are affected during the synthesis of these particles. It is undeniable that research and literature review on the toxicity of AgNPs are limited and therefore the exact concentration of AgNPs that is safe for human is still not established as results obtained and presented by different studies showed dual effects of AgNPs. Hence, further studies must be conducted to interpret comprehensively on the toxicity aspects of AgNPs to ensure safe use in the cosmeceutical field. The understanding on the mechanism of actions possessed by the particles will provide an opportunity for cosmetic manufacturers to venture into different and versatile applications for their inventions.

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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