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TOXICITY OF ZINC OXIDE NANOPARTICLES ON HUMAN SKIN DERMAL CELLS

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ABSTRACT

Zinc oxide (ZnO) has special physical and chemical characteristics which enable it to be utilized in numerous applications including electronics, sunscreens, pigments, and most notably in biomedical applications. Nanoemulsions containing zinc oxide nanoparticles (ZnO NPs) are progressively sought-after as an active component in cosmetic formulations and are used in sunscreens, moisturizers, and antiaging products. Zinc paste bandages including Unna boot consist of open wove cotton gauze treated with ZnO paste are now common medicaments for leg ulcers. The damaged and broken skins are vulnerable to ZnO NPs uptake. This being the case, ZnO NPs on the skin surface can affect the functions of surrounding cells in numerous ways by penetrating into the skin cells. This could exert toxicity effects on the skin cells over time depending on the concentration and site of ZnO NPs exposure. This review brings together some findings regarding the toxicity of ZnO NPs on human skin dermal cells and thus in turn enlightens the safer usage of ZnO NPs in skin care applications.

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1 Introduction

Richard Feynman, the Nobel Prize winner in 1959, was the foremost to foresee the advent of modern technology that might work with materials on just a range of 1–100 nm. Nanotechnology's true promise lies in the potential for manipulating materials at the same unimaginably small scale (Tocco et al., 2012). The reverberations that nanotechnology has in our lives at this moment in time are mountainous. Current implementations contribute to the instigation of devices, systems, and structures that are capable of revolutionizing medical therapeutics and diagnostics which have yet to be seen (Rajeshkumar et al., 2019). According to a study from the Consumer Product Inventory of Nanotechnology, silver nanoparticles (Ag NPs) are the most commonly used nanomaterials as they are present in 435 (24%) consumer products on the market (Therapeutic Goods Administration, 2006; Vance et al., 2015; Zhang et al., 2016).

Most of the metal nanoparticles (MNPs) such as copper oxide, magnesium oxide, silver, and zinc oxide nanoparticles exhibit antimicrobial properties that have been imparted into the packaging to kill harmful microorganisms (Makhlouf &Tiginyanu, 2011). In this regard, antimicrobial MNPs have positive results in hindering food deterioration as well as prolonging food's shelf life because of the intrinsic physicochemical properties of inorganic MNPs which enable the unrestrained development of reactive oxygen species (ROS) that primes to oxidative stress and ensuing cell damage (Fu et al., 2014). Given their low toxicity, price, and ultraviolet barrier properties, zinc oxide nanoparticles (ZnO NPs) are favored over Ag NPs (Chaudhry et al., 2008; Llorens et al., 2012). Drug delivery has drawn awareness of researchers and pharmaceutical companies that nano-mediated systems could constitute an acceptable exchange therapy for conventional drugs since they can provide a more impactful drug build-up in the site of infection with reduced side effects (Grumezescu, 2016).

2 Zinc Oxide Nanoparticles

Since the early 1960s, ZnO has been synthesized in thin films to be used as catalysts, sensors, and transducers. Due to its distinctive and precise properties, ZnO has attracted attention for a broad array of applications like those of electrical conductors, optical (pigment applications), and thermal since it is stable at temperatures more than 1800°C (Moezzi et al., 2012). Zinc oxide nanoparticles (ZnO NPs) are also known as oxydatum, ketozinc, permanent white, zincioxicum, and oxozinc (AZoNano, 2013). ZnO NPs have inherent qualities determined primarily by size, crystallinity, composition, and morphology. Their characteristics, such as morphological, chemical, and mechanical features, alter concerning the nanometer level. In addition to the stated properties, ZnO NPs also have a high electrochemical coupling coefficient, high chemical stability, and high photostability (Kołodziejczak-Radzimska & Jesionowski, 2014). Not only ZnO NPs work as credible physical ultraviolet A (320-400 nm) as well as ultraviolet B (290-320 nm) filters (Nohynek et al., 2007; Zvyagin et al., 2008) that are present in sunscreens to shield users from the damaging outcomes of UV rays (Maverakis et al., 2010; Djearamane et al., 2019), it also reduces the reliance on systemically absorbable chemical sunscreen agents (Gonzalez et al., 2006). These formulations aimed to shield the skin from sun-induced erythema, decrease photoaging as well as possibly decrease the likelihood of skin cancer (Holmes et al., 2016) by lingering at or close by the surface of the skin because there is no reasoning for their entry into the skin (Gamer et al., 2006; Cross et al., 2007). However, contact with ZnO NPs through the usage of consumer products and also through occupational and environmental exposure might bring health hazards to humans.

3 Toxicity of ZnO NPs on Skin Cells

The skin as the body's key defence organ is well equipped to halt the penetration of materials through its surface (Lin et al., 2015). Mammalian skin is divided into many layers: stratum corneum (SC), epidermis, dermis, and subcutaneous layer. SC is the barricade that limits the penetration rate of many topically applied materials (Schaefer et al., 2003). Nanomaterials including nano-emulsions made up of oils, emulsifiers and aqueous vehicles are being processed to create a stable network of nano sized globules that are increasingly popular in cosmetics and medicine (Nohynek et al., 2007). For instance, the Nano Gel platform developed by Tri-K Industries presents a simplistic production process for refined nanoemulsion products that prevents transepidermal water loss (TEWL) and enables it suitable for many applications including anti-aging products, moisturizers, and sunscreens (Müller et al., 2002).

Zinc is an essential micronutrient for human health (Rostan et al., 2002). Zinc has a prominent part in influencing each stage of the wound alleviating phase; from membrane restoration, oxidative stress, coagulation, inflammation, and immune response, tissue re-epithelialization, angiogenesis, to scarring (Sekhon & Sen Gupta, 2017). Zinc is particularly essential to the skin (Rostan et al., 2002) because the skin contains high zinc in the epidermis (Gupta et al., 2014). Because of its multitude in the epidermis, a slight zinc inadequacy can lead to coarsened skin and hinder the curing of wounds (Lansdown et al., 2007). Unna boot bandages of zinc paste comprised of open wove cotton gauze infused with ZnO paste persist as the traditional procedure for leg ulcers (Williams, 1999).

Numerous factors possibly influence the absorption of ZnO NPs into the skin following its superficial application. Firstly, the surface area to volume ratio increases with smaller NP's that enhances the reactivity of NPs with penetration capacity into the

skin. The amount of cellular uptake of NPs increases with the decrease of size as the submicron ZnO or ZnO microparticles penetrate slower than ZnO NPs (He et al., 2010; Reed et al., 2012). Secondly, the type of zinc ion formed following ZnO dissolution and then readiness to penetrate into the skin cells is pH-dependent. The rate of dissolution of ZnO into Zn^{2+} is faster at lower pH (Han et al., 2010; Bian et al., 2011). Thirdly, high pH (>9) or low pH (<3) damages human skin integrity which brings the risk of NPs entry into the skin cells (Holmes et al., 2016). Fourthly, the capability of zinc ions and ZnO to traverse the SC is reliant on the essence of their engagement with the SC (Hostynek, 2003). The noticeably elevated uptake of Zn in human skin at lower pH occurred because human SC is semipermeable for cations as Zn is in the cationic form at lower pH (LareseFilon et al., 2011). Lastly, in the topical formulations, zinc absorption into the skin cells is determined by the concentration of zinc present in the topically applied substance (Zhong, 2004).

The controversy regarding the safety of ZnO to humans began in the late 1990s when ZnO had been utilized for obstructing UV radiation in sunscreens. Studies indicated that ZnO NPs cannot cross the skin barrier, so it stays on the skin's external layer and therefore does not cause toxicity (Klingshirn, 2007; Moezzi et al., 2012). Furthermore, ZnO NPs pooled on the exterior of skin and inside the skin furrows through the intact epidermis have not been reported to penetrate or cause cellular toxicity. Mohammed et al. (2019) also concluded the safe use of sunscreen products. However, the dermal absorption of ZnO has been documented with a ZnO cream (Triple Treatment, Smith & Nephew, Hull, UK) administered on the forearm for a duration of 3 hours (Gorodetsky et al., 1999). Another report showed low zinc ion uptake by skin in normozincemic humans through topical ZnO (Hostýnek et al., 1993). When the superficial keratinocytes are shed off naturally, the zinc ion in the epidermal keratin will be gone while a portion of zinc entering deeper skin layers will then be taken up into the circulatory system (Lansdown et al., 2007). Although topically spread ZnO does not enter the viable epidermis, ZnO hydrolyzes on the skin superficial, which raises the zinc ion concentration in SC and the epidermis, thus in the systemic circulation as well as in urine (Holmes et al., 2016). It has been mentioned that little quantities of zinc from ZnO do get absorbed through the human skin (Hayden et al., 1997). Zyyagin et al. (2008) demonstrated that the caprylic capric triglycerides formulation of ZnO NPs encouraged the passive diffusion of NPs through the lipophilic intercellular passage. This passage depicts the fundamental transdermal penetration pathway. ZnO NPs mineral constituents are found on the skin barrier as well as in the region of desquaming corneocytes as shown by electron micrographs of human skin (Zvyagin et al., 2008; Espitia et al., 2012). At lower pH, more ZnO undergoes acid-catalyzed hydrolysis to liberate zinc ions. Zn^{2+}will be the main ion in the solution and that zinc ion penetrates the SC and thence into the viable epidermis (Bian et al., 2011). An insoluble precipitate forms at pH 9 as the zinc is in the $Zn(OH)_{2(s)}$ form because of the existence of a zero charge point at around pH 9.4. Hence, the amount of zinc ions accessible to pass through the skin is lesser at higher pH due to a decrease in $Zn(OH)^{+}$ ions dissolution (Holmes et al., 2016). The uncertainty now is if the rise in free zinc may affect the intracellular zinc homeostasis. Studies on the toxicity of skin cells by differing labile zinc concentrations are doubtful. It turned out to be that the viability of human skin fibroblasts with the company from oxidative stress from UVB as well as UVA radiation has been assisted with the rise in intracellular zinc (Richard et al., 1993).

The clinical relevance of the transdermal route in alleviating the symptoms of zinc deficiency is uncertain. After covering the extensive skin areas using topical ZnO in petrolatum, neither Morgan et al. (1980) nor Derry et al. (1983) managed to track an elevated serum zinc level. Systemic zinc uptake by topical zinc is significantly enhanced in the absence of a skin barrier. Following the usage of ZnO-medicated adhesive dressing, serum zinc concentration elevated was reported among the victims of substantial partial-thickness as well as a full-thickness burn injury. There were no substantial variations in serum zinc among ZnO-treated and control-treated patients with small wounds about $10cm^2$ (Lansdown et al., 2007). Skin diseases like psoriasis vulgaris produce hyperkeratosis that might end in reduced topically applied substance uptake (Korting et al., 1990). This is reasoned by the thickening of the epidermis as a result of inflamed skin which ultimately enhances the skin as a barricade (Walker et al., 2003). Other skin diseases such as eczema and podoconiosis (elephantiasis) with rupture in the SC permit the penetration of topically applied substances as the reduction in the barrier capacity of the skin (Korting et al., 1990). Hence, the studies have confirmed that the damaged skin is susceptible to ZnO uptake (Williams, 1999, Walker et al., 2003, Lansdown et al., 2007). Earlier studies reported that exogenous zinc ions are useful as they can avoid herpes infections (Read et al., 2019) and serve to shield the skin as an antioxidant (Prasad, 2014). Two modes of action involving zinc ions applied topically as an antioxidant was suggested. Firstly, Zn^{2+} substitutes Fe^{2+} and Cu^{2+} on cell membranes along with proteins. Secondly, Zn^{2+} might stimulate metallothione in forming a zinc-thiolate moiety that operates as a chelating agent for damaging free radicals (Rostan et al., 2002). In a hamster ear experiment, the topical formulation of zinc ions was proven to simulate metallothionein. The skin contains metallothionein, which will cling to additional labile zinc to ensure an ideal concentration of zinc ions. Small concentrations of free zinc originating from ZnO that enter intact skin may be advantageous to serve as an antioxidant (Morgan et al., 1993).

Besides, when ZnO NPs undergoes hydrolysis, it produces zinc ions and reactive oxygen species (ROS). This further activates different cytotoxic pathways such as intracellular calcium flux, plasma membrane leakage, and mitochondrial depolarization (George et al., 2009).

Conclusion and Recommendation for Future Research

From the earlier study findings, it is evident that ZnO NPs do not penetrate the intact healthy skin and therefore do not cause toxicity effect. On the other hand, some studies have reported the penetration of zinc ions through the stratum corneum of damaged and compromised skin. The information regarding the toxic effects of ZnO NPs in skin cells is scarce. Therefore, future research studies are needed in both *in vitro* and *in vivo* to address the dose and duration of exposure required causing the potential toxic effects of ZnO NPs upon entry into the skin cells.

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