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Review article

Inorganic nanoparticles in dermopharmaceutical and cosmetic products: Properties, formulation development, toxicity, and regulatory issues

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ABSTRACT

The use of nanotechnology strategies is a current hot topic, and research in this field has been growing significantly in the cosmetics industry. Inorganic nanoparticles stand out in this context for their distinctive physicochemical properties, leading in particular to an increased refractive index and absorption capacity giving them a broad potential for cutaneous applications and making them of special interest in research for dermopharmaceutical and cosmetic purposes. This performance is responsible for its heavy inclusion in the manufacture of skin health products such as sunscreens, lotions, beauty creams, skin ointments, makeup, and others. In particular, their suitable bandgap energy characteristics allow them to be used as photocatalytic semiconductors. They provide excellent UV absorption, commonly known as UV filters, and are responsible for their wide worldwide use in sunscreen formulations without the undesirable white residue after consumer application. In addition, cosmetics based on inorganic nanoparticles have several additional characteristics relevant to formulation development, such as being less expensive compared to other nanomaterials, having greater stability, and ensuring less irritation, itching, and propensity for skin allergies. This review will address in detail the main inorganic nanoparticles used in dermopharmaceutical and cosmetic products, such as titanium dioxide, zinc oxide, silicon dioxide, silver, gold, copper, and aluminum nanoparticles, nanocrystals, and quantum dots, reporting their physicochemical characteristics, but also their additional intrinsic properties that contribute to their use in this type of formulations. Safety issues regarding inorganic nanoparticles, based on toxicity studies, both to humans and the environment, as well as regulatory affairs associated with their use in dermopharmaceuticals and cosmetics, will be addressed.

Abbreviations: **AgNP**, silver nanoparticle; **Ag@ZnO**, silver nanoparticles coated with zinc oxide; **Al_2O_3**, aluminum oxide; **AuNP**, gold nanoparticle; **BP-4**, benzophenone-4; **CNC**, cellulose nanocrystal; **CuNP**, copper nanoparticle; **CuONP**, copper oxide nanoparticle; **HaCaT**, human keratinocytes; **NHEK**, normal human epidermal keratinocytes; **noSiQDs**, (NH, OH)-functionalized silicon quantum dots; **NP**, nanoparticle; **ROS**, reactive oxygen specie; **SiO_2NP**, silicon dioxide nanoparticle; **SiQDs**, silicon quanto dots; **SNP**, sílica nanoparticle; **SPF**, sun protection factor; **SC**, stratum corneum; **TiO_2**, titanium dioxide; **ZnO**, zinc oxide; **UV**, ultraviolet.

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1. Introduction

Cosmetics cover a broad portfolio of products which are typically classified as hair care, face care, antiperspirants, nail care, and skin care [1]. These products are made up of basic ingredients that serve as a vehicle for the products like cream, sunscreens, shampoo, and conditioner, among others. The utilization of nanoparticles - inorganic and organic - in cosmetics is becoming quite popular these days.

Globalization has increased the range of cosmetic products starting from basic products like toothpaste to products using modified-release technology and nanotechnology, becoming an indispensable part of personal well-being. The cosmetic formulations presented as a base or vehicle have properties such as protection, cleanser, hydrating, moisturizing, soothing, and firming [2]. For some time now, men and women have been using cosmetics for cleaning, beauty, or other reasons. In addition, the growing media coverage of these products makes people more informed and aware of their existence and functionalities. This has further increased the market for cosmetic products. The projected Compound Annual Growth Rate (CAGR) for 2018–2023 (7.14 %) and the expected market value in 2023 (USD 805.61 billion) attest to this [3]. In addition, the rapid rise in improved life expectancy led to the evolution of beauty standards leading to the development of high-quality products with a very high revenue-generating market estimated to be $716 billion by 2025 [4].

As with all dermopharmaceuthical products, cosmetics also face mechanical barriers in the skin. The stratum corneum (SC), the tight junctions in the interfollicular epidermis and the hair follicles are crucial in this context and have to be considered when developing formulations for topical application. The SC is the most external mechanical barrier and is considered the first obstacle to external aggression. It plays an important role in the absorption of substances by passive diffusion. Next, in the stratum granulosum are the tight junctions, which are considered the second barrier of the epidermis, where substances cross mainly via the paracellular route. In addition, hair follicles have also shown good absorption and are considered good potential targets for drug delivery [5]. Like many other industries, nanotechnology has made significant inroads into the cosmetics industry. This is because nanomaterials have numerous advantages such as increased surface area, good stability, high encapsulation efficiency, and loading capacity, prolonged retention time, and site-specific delivery [3]. In cosmetics, inorganic nanoparticles, in particular, are widely used, rather than organic nanoparticles, because of their hydrophilicity, biocompatibility, stability, and non-toxicity [6]. One another major advantage of inorganic nanoparticles is their easy surface modification leading to a wide range of formulations providing cosmetic effects while at the same time reducing the chances of side effects. Inorganic nanoparticles are able to overcome the concerns of organic nanoparticles, particularly less irritation, itching, and allergy to the skin and have higher chemical stability. In this sense, inorganic nanoparticles are assuming a prominent position in dermopharmacy, as well as in the cosmetics industry, one of the most stringent segments of the economy worldwide. In addition, these advantages are complemented by the fact that they are cheaper to produce [7]. This manuscript discusses the main physicochemical properties of inorganic nanoparticles, explaining in detail the relationship with their applications in dermopharmaceuticals and cosmetics. For this purpose, we evaluate the most described inorganic nanoparticles in this field to date – particularly, titanium dioxide, zinc oxide, silicon dioxide, silver, gold, copper and aluminum nanoparticles, nanocrystals and quantum dots. Their unique and varied properties have been of great interest in this area of research for their incorporation into topical medicines as skin ointments, and sunscreens, lotions, among others.

Sunscreens found wide applications in cosmetic industries as UV (ultraviolet) protectants or blockers against both UVA and UVB radiations. The formation of reactive oxygen species (ROS), resulting from exposure to this radiation, causes damage to the skin, including the destruction of collagen fibers and a decrease in skin elasticity. [8]. Dermatologists guide individuals to use sunscreen, as they believe that it provides protection against skin cancer like actinic keratoses and squamous cell carcinoma [9]. Inorganic metals like titanium dioxide (TiO_2) and zinc oxide (ZnO) are essential in the cosmetics industry for the production of opaque inorganic sunscreens [10]. The sizes of ZnO and TiO2 range from 200 to 400 nm and 150–300 nm, respectively. These particle sizes promote a white, floury texture on the skin surface, which is noticeable in black skin persons [11]. So, there arises a demand to solve these cosmetic limitations regarding consumer satisfaction to reduce the particle dimensions encouraging new formulations, culminating in the use of nanoparticles with size < 100 nm [12]. These sizes are small and unable to be detected by a conventional microscope allowing smooth texture that can be applied transparently without any noticeable appearance giving photoprotection by absorbing UV radiation [13 14]. Inorganic UV filters such as TiO_2 and ZnO act as potential active photoprotective sunscreens as ZnO absorbs broad UVA-UVB rays whereas TiO_2 better works in UVB protection [15]. According to Wang et al. [10], both TiO_2 and ZnO nanoparticles exist in three different physical forms as shown in Fig. 1.

Nowadays, sunscreens containing ZnO and TiO_2 are preferred over organic compounds, due to the fact of dual blocking of UVB and UVA radiations with additional advantages offered like microsize opaque particles can be reduced to nanosize without compromising their UV blocking efficacy [16]. Further, these inorganic sunscreens provide supremacy by using inert base materials, and limited skin sensitivity by penetration only up to the dermis layer, hence less irritation and broad spectrum UV rays protections [17]. But it is not simple for any chemicals to penetrate the skin as naturally many barriers are present on the skin which avoid their entry into the skin dermis and epidermis as reviewed by Three G et al. and presented in the next diagrammatic representation (Fig. 2) [18]. Also, ZnO and TiO_2 nanoparticles are explored for their applications in wastewater treatment and the effective photocatalytic degradation of azo dyes. In agriculture, they have wide uses in increasing crop productivity, as stress resistance and plant growth promoters [19,20,21].

The benefit of using nanoparticle-formulated nanocarriers is easy penetration through the SC by the transappendagael route (Fig. 3A) which uses dermis hair follicles, sebaceous, and sweat glands (with a hydrophilic pore diameter of $5x10^4$ nm). The other two pathways are paracellular (Fig. 3B) (through the gaps between the cells, facilitated by the ceramides unsaturated liquid domains with 13 nm phase), through inter-corneocyte having pore size 0.5–7.0 nm to 20–30 nm, and minor transcellular (Fig. 3C) (passing through the cells) route which is insignificant due to highly impermeable cornified skin barrier [22,23]. The

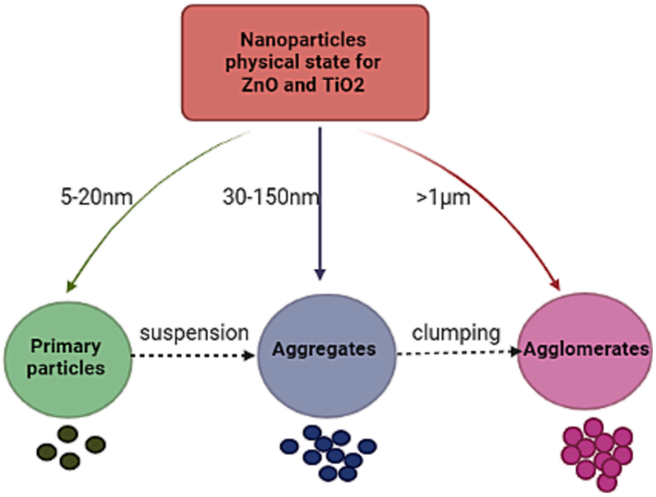

Fig. 1. Different forms of nanoparticles are classified according to their size and physical properties.

interactions of nanocarriers and SC increase both the fluidity and polarity of lipids present in the structure, which aid in weakening the barrier effect to amplify the penetration of nanoparticles used in formulations [24].

The main concerns surrounding the use of nanoparticles focus on safety related to their penetration into the skin, changes in physicochemical properties under the effect of light, and their efficacy on damaged skin, whose published reports are scarce and require urgent attention [22,25].

Since ancient times, silver (Ag) (silver ions/silver-based compounds) has been used in the treatment and management of various diseases due to its recognized therapeutic capabilities, in particular its bactericidal and antimicrobial properties [26]. Additionally, there are no reports of side effects on human health on the usage of silver at nominal and reasonable concentrations [27]. Ag nanoparticles have become of great interest in the field of research largely due to their unique activity against a wide variety of microorganisms, making them an effective solution to resistance to commonly used antibiotics [26]. Usually, for antimicrobial activity, silver nitrate ($AgNO_3$) is the most used form. However, the silver nanoparticles, due to their larger surface area, are shown to be more beneficial than silver in their free form, since a larger surface area also provides greater exposure to microbes [26]. Over 50 % of global nanoparticles' (NPs) production is accounted for by silver nanoparticles and these are intensively explored nanostructures [26]. Silver nanoparticles between 1 and 100 nm are the most widely used for biomedical applications, particularly wound dressings, drug delivery carriers, tissue support, and coating applications [26,27]. The use of silver nanoparticles in cosmetics can improve UV radiation absorption without any toxicity to the skin as they show good photoprotective activity, are widely used in sun-protective skin creams, and ointments, and have antimicrobial properties. In addition, they are used in air, water, and surface disinfection, besides being environmentally friendly [28].

Silicon dioxide nanoparticles (SNPs) have gained considerable attraction in the cosmetic industry due to their hydrophilic properties. SNPs can enhance the shelf-life and the effectiveness and texture of the products (cosmetics). Its superb absorption and anti-caking properties are used in cosmetic powders, together with its unique pigment distribution are well used in lipsticks. The usage and exposure of SNPs are still limited and exposure tests are needed [6].

On that note, gold nanoparticles (AuNPs) showcase excellent optical properties, surface plasmon resonance, and photothermal properties [29]. Copper/copper oxide (Cu/CuO) nanoparticles show antimicrobial and wound-healing properties, so they have also been of interest to be used in cosmetics [30,31]. Alumina nanoparticles are utilized as coatings to improve photostability over different cosmetic formulations [32]. Nanocrystals have high saturation solubility and dissolution velocity making them the obvious choice for poorly soluble active cosmetic ingredients [33]. Nowadays, quantum dots are being explored further in cosmetics due to their remarkable optical qualities. Their suitability to interact with UV light is being used favorably in sunscreens and other cosmetic active ingredients [34].

In general, nanocarriers are effective drug delivery systems in cosmetics since their unique small particle size allows them to cross biological barriers, minimize degradation and maintain the amount of drug to be delivered to the target tissue site [35]. All the nanocarrier delivery systems offer great advantages due to their physicochemical properties which enhance the solubility and bioavailability of hydrophobic drugs, protect against enzymatic degradation by acting as a protectant carrier system, and increase the circulation time ultimately improving the therapeutic benefits [36]. Vesicular nanoparticles, like liposomes, show several limitations like poor stability and penetration, although improved vesicles like ethosomes, transfersosmes, and niosomes are advanced nanocarriers that are cheaper, available, lasting improved superior penetration power [37,38,39]. Despite these advantages properties, inorganic nanoparticles are incomparable as they have broader surface conjugation chemistry, schematic simplistic preparation, are non-greasy, and easily absorbed with outstanding biocompatibility with no toxicity to living tissues, which makes them suitable candidates for the cosmetic industries [40].

However, concerns remain about the health, safety, and toxicity risks

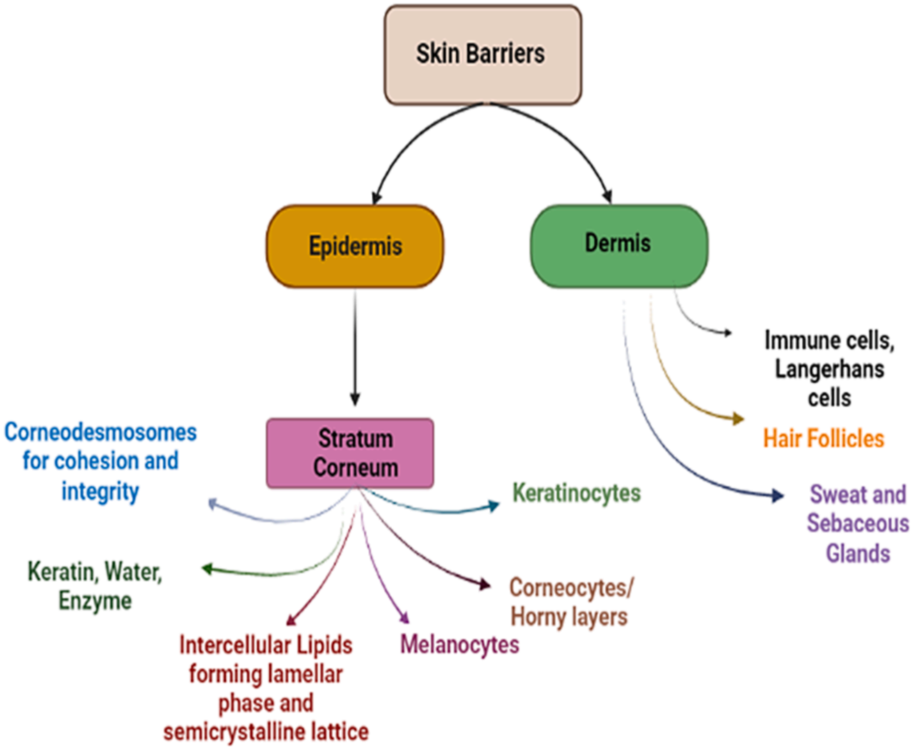

Fig. 2. The flow chart represents different skin barriers present naturally (epidermis and dermis), made up of various types of cells that prevent penetration of chemicals into the skin.

of using these nanoparticles in cosmetics, as well as the regulations followed by countries to ensure the production and marketing of safe, quality products from the manufacturer, as well as steps taken to educate the consumer. This review aims to address the most current research on the use of inorganic nanoparticles in cosmetic products.

2. Inorganic nanoparticles used in cosmetics

Fig. 4 is intended to summarize and highlight the types of inorganic nanoparticles that are most commonly used in the field of cosmetics and Table 1 summarizes the main characteristics of inorganic nanoparticles and information about their use in cosmetic products.

2.1. Titanium dioxide nanoparticles

Naturally, three crystalline structures are available for TiO_2 namely rutile (most stable), anatase, and brookite. These crystals show significant optical properties of refractive indices 4.0 and 3.6 for rutile and anatase polycrystalline films respectively, which offer them their characteristic white pigment making them suitable components for cosmetic purposes [62]. TiO2 is a semiconductor material consisting of a differentiated electronic structure comprised of three important bands namely low energy valence bonds which are filled with electrons, and high energy conduction bands comprising holes, and in between these two bands is the band gap [63]. The crystalline structure of titanium oxide is formed among the O-2p with Ti-3d orbital state. When the high-energy photons fall on the rutile or anatase crystalline structure whose energy exceeds or equalizes the incident photon energy, results in the jumping of the valence band electron to the conduction band electron. The absence of electrons promotes the formation of holes which is localized electron vacancy involved in characteristic photoexcitation of the electron-hole pairs that is involved in redox reactions on the crystal surface. The band gap energy is < 3.03 eV and < 3.2 eV value determined for rutile and anatase crystalline form respectively.

The main steps engaged in the photocatalytic process are a generation of photons, separation of the bands, recombination of the electron/holes, and their subsequent surface capture where two half redox reactions occur with oxidation of photo-generated holes and reduction of photo-generated electrons [64]. A detailed mechanism of the specific steps is explained in Fig. 5 which elaborates on the specific process. A large part of the e/h + might recombine or move to the surface of the nanoparticles, which dissipates the absorbed energy in the form of light, heat, and the production of ROS. The remaining electron and hole pairs not involved in the recombination migrate toward the surface, leading to the production of hydrogen peroxide and superoxide anion which can impair cell function [65].

The following table (Table 2) gives the various properties of the formulations and the results of their dermal exposures. It is important to note that depending on the size, type of formulation, structure, type of study conducted, and skin conditions (intact or damaged), different results in terms of penetration are observed. These studies show that several factors have to be taken into account when evaluating the results of dermal exposure to nanoparticles, highlighting the need for a case-by-case assessment.

Henceforth nowadays, the concept of synthesis of green TiO_2 NPs from Moringa oleifera leaves has shown significantly better antiseptic properties, likewise, Yu et al. used natural lignosulfonate macromolecule, to exhibit surface modifications increasing the efficiency as UV blocker sunscreens help in neutralizing free radicals and help as natural sun blockers with 30–60 % higher sun protection factor (SPF) compared with the inorganic nano grade nanoparticle [70,71].

The first industry using nano-based ingredients was the cosmetics industry, which used intentionally manufactured nanomaterials with 1–100 nm dimensions [72]. In 1986 the first liposomes-based anti-aging cream Capture^{TM} was launched in the market, subsequently, various world-famous brands used nanomaterials in skincare cosmetics [73]. The main targets of nanomaterials are they provide greater surface area allowing efficient transport, penetration, and delivery, the introduction of new colors in lipsticks and nail polishes, endure lasting effects in makeups, and are effective UV blockers with crystal clear translucent effect on every skin type [6]. TiO2 nanoparticles are one of the main ingredients used in these cosmetic preparations which are very popular

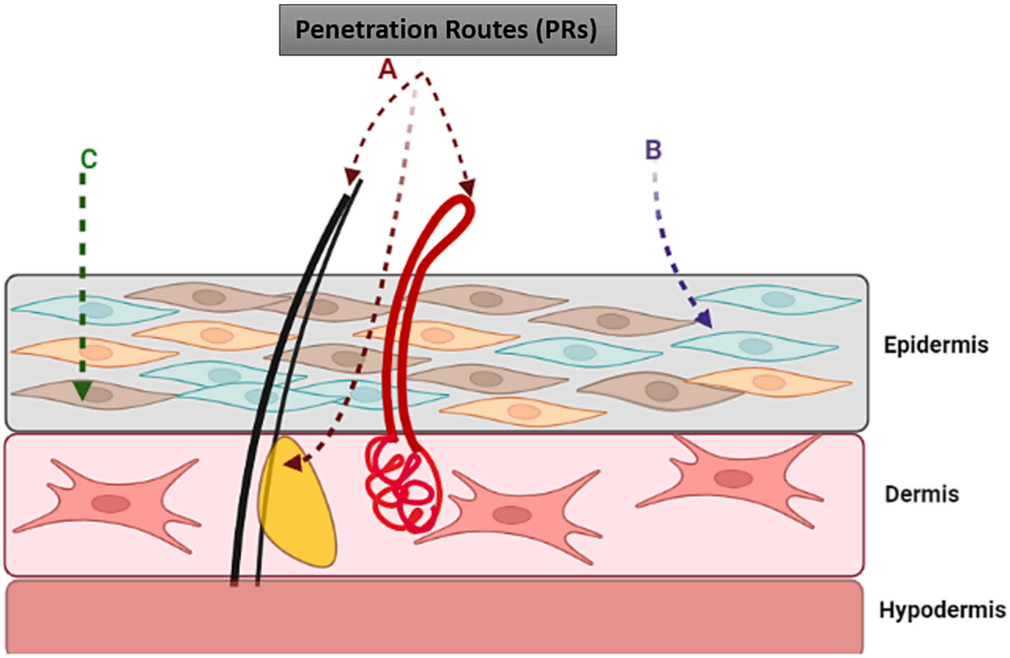

Fig. 3. Main layers of the skin (epidermis, dermis, and hypodermis) and the routes of the penetration of nanoparticles. The epidermis shows different cell types like corneocytes, keratinocytes, and melanocytes. The second layer comprises immune cells like Langerhans cells (pink star), hair shaft (black), sebaceous gland (yellow), and sweat gland (red coiled structure). Furthermore, the figure represents the three main routes of nanoparticle delivery A) Transappendagael, B) Paracellular, and C) Transcellular.

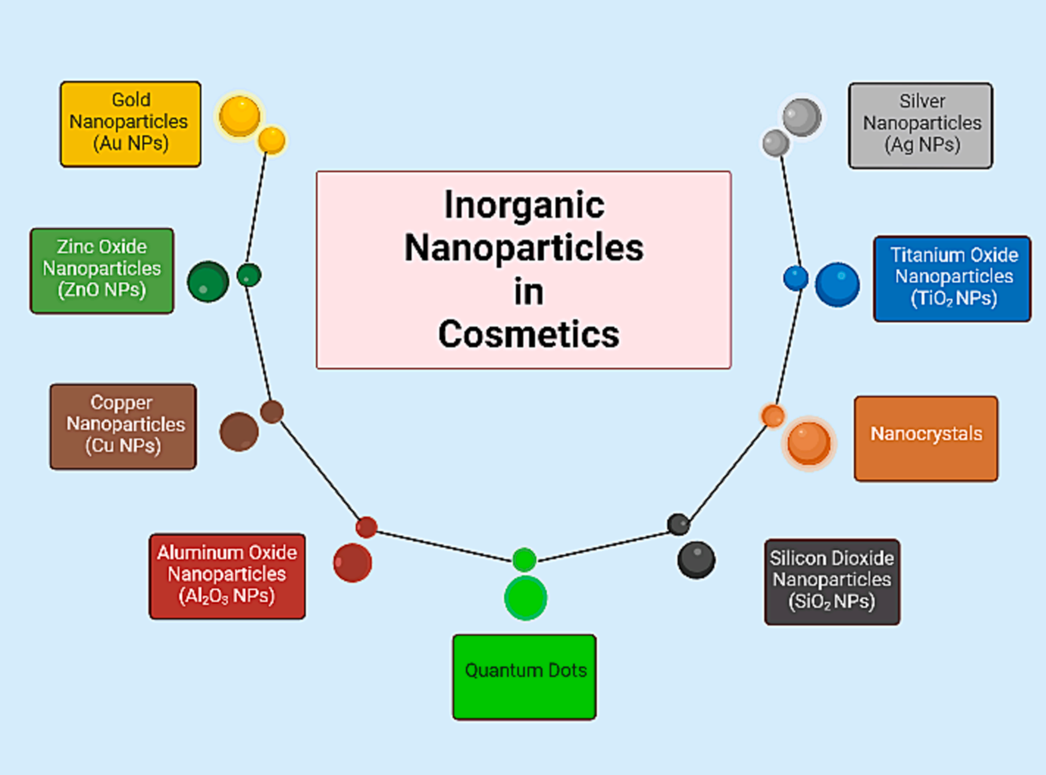

Fig. 4. Main inorganic nanoparticles involved in cosmetic enhancement.

and demanding brands among consumers.

2.2. Zinc oxide nanoparticles

Zinc oxide is naturally present in the earth's crust as two different shapes of crystalline ZnO, namely wurtzite (common and stable form) and zinc blende. ZnO is an n-type semiconductor. A spectroscopic ellipsometry analysis done by researchers has reported the indices of optical refractive which range from 2.3 to 2.0 values in 375–900 nm suggesting a lower whitening effect as compared to TiO_2. The band gap energies calculated for Wurtzite and Zinc blende are approximately equal to 3.22 eV and a higher value of 3.32 eV respectively [74].

UV attenuation by these inorganic sun blockers mainly rutile and anatase TiO_2, and wurtzite ZnO with sizes ranging from 0.1 to 10.0 nm results from the reflection and dispersion of UV radiation complementarily absorbing UVB (TiO_2) and UVA (ZnO) rays through the above mentioned described physicochemical properties [75]. The smaller particle size of nearly 100 nm for TiO_2 and 200 nm for ZnO increases the surface atoms solving the undesirable properties of opaqueness by influencing the band gap width ultimately changing the spectral shift, transmitting more visible light, and aiding transparent appearing particles [76]. Another point to be considered is the surrounding medium like pH and ionic strength which leads to aggregation of the nanoparticle, leading to an increase in size and hence decreasing the band gap energy which results in loss of UV attenuation properties over time in the formulated sunscreens [77]. Further, according to the Mie theory which determines the relationship between particle size and UV attenuation property, nanoparticles aggregations lead to 8 % lower UV attenuation in contrast to single spherical rutile TiO_2 particles [78].

L'Oreal S.A, one of the biggest world-famous brands has achieved maximum patents ranking sixth in the market use of ZnO nanoparticles in their many products, whereas Shiseido has limited the use of ZnO in emulsion-based formulas used in gels, lotions, and creams with the ultimate goal of enhancing the moisturizing power [79,80]. In fact, an increase in transepidermal water-loss and a decrease in the skin's water content have been reported when ZnO-based formulations are applied [81].

2.3. Silicon dioxide nanoparticles

Silicon dioxide nanoparticles (SiO_2NPs) are an alternating mixture of silicon and oxygen atoms. These nanoparticles are $<$ 100 nm in dimension. They are also known as nanostructured sílica, sílica nanoparticles (SNPs) or nano-silica. These are stabilized as nanodispersions with a range of 5–100 nm. Silicon dioxide nanoparticles have been an important component in cosmetic formulations, but also as drug carriers due to their properties such as hydrophilic nature, low-cost synthesis, and magnificent biocompatibility. These are often recognized as rinse-off and leave-on cosmetic products for hair, and face [6]. These nanoparticles contribute to a better texture and spreadability of the lipsticks and these fine particles won't invade the liplines [82]. This often increases the texture, and shelf-life of the product as it enhances the absorbance and works as an anticaking agent.

Silicon has excellent dispersion properties, its formulations contain an oily or greasy feel on the skin. These are also used in emulsions as sunscreens and can improve water resistance and provide spreading of physical and chemical filters thereby increasing their SPF levels in sunscreens. Considering this effect, SNPs are seen as enhancers and promoters of the effects of sunscreens, increasing their effectiveness. These are available in emulsion form and have improved retinol resistance to UV-induced degradation [83].

There are few studies depicting that silica microparticles that possess a size of 3 μm are capable of penetrating the living epidermis and even with 65 % ethanol concentration able to enter the dermis, this has initiated the utilization of carriers in which silica particles can be transported. The utilization of SNP coated nanoemulsions especially oil in water were utilized for stabilization and penetration of lipophilic agents. Lecithin and oleylamine are generally utilized to provide negative and positive charges to the formulation. These have improved the resistance properties of retinol to degradation [84].

Table 1
Main characteristics of inorganic nanoparticles for use in cosmetic products.

Nanoparticles	Dimensions (nm)	Properties	Cosmetic applications	Route of exposure	*In vitro* toxicity	*In vivo* toxicity	Ref.
Titanium dioxide	15–40	Photocatalytic	Sunscreen	Dermal	Observed only at higher concentrations	NO	[41]
	10–50	Antimicrobial	Creams	Skin	Cytotoxicity	NA	[42]
Zinc oxide	8–47	Scatter UVA and UVB rays	Sunscreen	Dermal	Safe	Non-toxic	[184344]
Silicon dioxide	400–700	Hydrophilic	Hair conditioner	Hair shafts	Cytotoxicity tests are done	Observed in cell lines	[45]
Silver	20,40,90	Protective effect on the skin from UVB-radiation	Sunscreen	Skin application	NO	NO	[46]
	15	Antimicrobial, antifungal, antibacterial	Creams, ointments, soaps, anti-dandruff shampoos, sunscreens	Skin cell lines	Observed	NA	[47]
GoldAu Nanosheets	< 60	NA	Facial cosmetics	Through hair follicles	NA	No systemic toxicity. No toxicity towards fibroblasts and keratinocytes. Affects hair growth.	[48]
- AuNPs-SS	8–20	Wound healing	Skin moisturizer	NA	No significant change in cell viability. Non-toxic.	NA	[49]
- Hubertia Ambavilla - AuNP	40–80	Antioxidant	Sunscreen	Skin Penetration	Non-toxic to fibroblasts and dermal cells.	NA	[50]
- P. Ginseng capped AuNPs	10–20	Antioxidant	Moisturizer	Skin Penetration	Non-toxic to dermal fibroblasts, melanoma cells	NA	[51]
- Arbutin-AuNPs	10–20	Anti-inflammatory	Skin whitening	NA	NA	Non-toxic	[52]
Copper	60–200	Anti-fungal, Anti-bacterial	Colorant	No penetration. Adhered to surface	Significant decrease in cell viability	NA	[53]
Aluminum oxide	5–50	Absorbant, Anti-caking agent	Soft Focus, Glow	NA	NA	NA	[54,55]
NanocrystalsSymurban	280	Better solubility, retention time	Anti-pollution agent	Skin penetration	NA	NA	[56]
- Rutin	300	Increased saturated, Solubility, Better diffusion	Facial cosmetics	Skin penetration	NA	NA	[57]
- Apigenin	413	Increased water solubility	UV protection	NA	NA	NA	[58]
- Hesperidin	150–500	Antioxidant	Face Cream (Anti-aging, Skin whitening, UV Protection)	Skin Penetration	Formulation A2 was found to be the safest. No toxicity was seen.	NA	[59]
Quantum dotsNH–, OH–functionalized Silicon QDs (noSiQDs)	4–6	Water soluble UV absorption	Sunscreen (Anti-yellowing)	NA	NA	NA	[60]
- (CdSe@CdS)-PEG	37	Fluorescence	Sunscreen	Intra-dermal	NA	NA	[61]
- Defect Rich ZnO QDs	385	Luminescence	Camouflage, Sunscreen	NA	NA	NA	[34]

Abbreviations: NA: Not available; NO: Not observed.

In some of the cosmetic ingredients along with SNPs, few additives are included in the formulations such as clay which provides a thickening consistency to the formulations [85]. There have been few advances in the utilization of SNPs as one of the major ingredients in hair care products. One study described a 206 nm size of SNPs as being able to penetrate the cortex and cuticle of bleached hair. Bleaching is the process where the hair loses the disulfide bond and also destroys the protein-rich surface. SNPs imbibition helps to interact with the protein surface with the hair cortex retaining a balance, and shows the retention of bleaching effect even after 13 shampoo washes [86]. The utilization of SNPs (core–shell) for attaining a density for the oil in water emulsions is important in many cosmetic formulations.

In the market, there are products, such as the Lancome Renergie microlift, manufactured by Lancome, used as an anti-wrinkle, which provides a possible lifting effect. Also, Primordial Optimum Lip, manufactured by Lancome, contains SNPs with a vitamin E combination that reduces lip wrinkles and fine lines [82].

2.4. *Silver nanoparticles*

Silver nanoparticles (AgNPs) are among the most used in cosmetic products. The usage of silver nanoparticles is approximately 12 % of all nanoparticles used in cosmetics [87,27].

In a study conducted by Kokura et al., 2010, the effects of silver nanoparticles were examined on microorganisms. In the same study, under UVB irradiation, skin permeability as well as cytotoxicity on human keratinocytes was evaluated. AgNPs were found to be extremely stable and exhibited suitable preservative activity against both mixed bacteria and fungi. Additionally, AgNPs were also found not to penetrate normal human skin. In this sense, it was considered that AgNPs seem

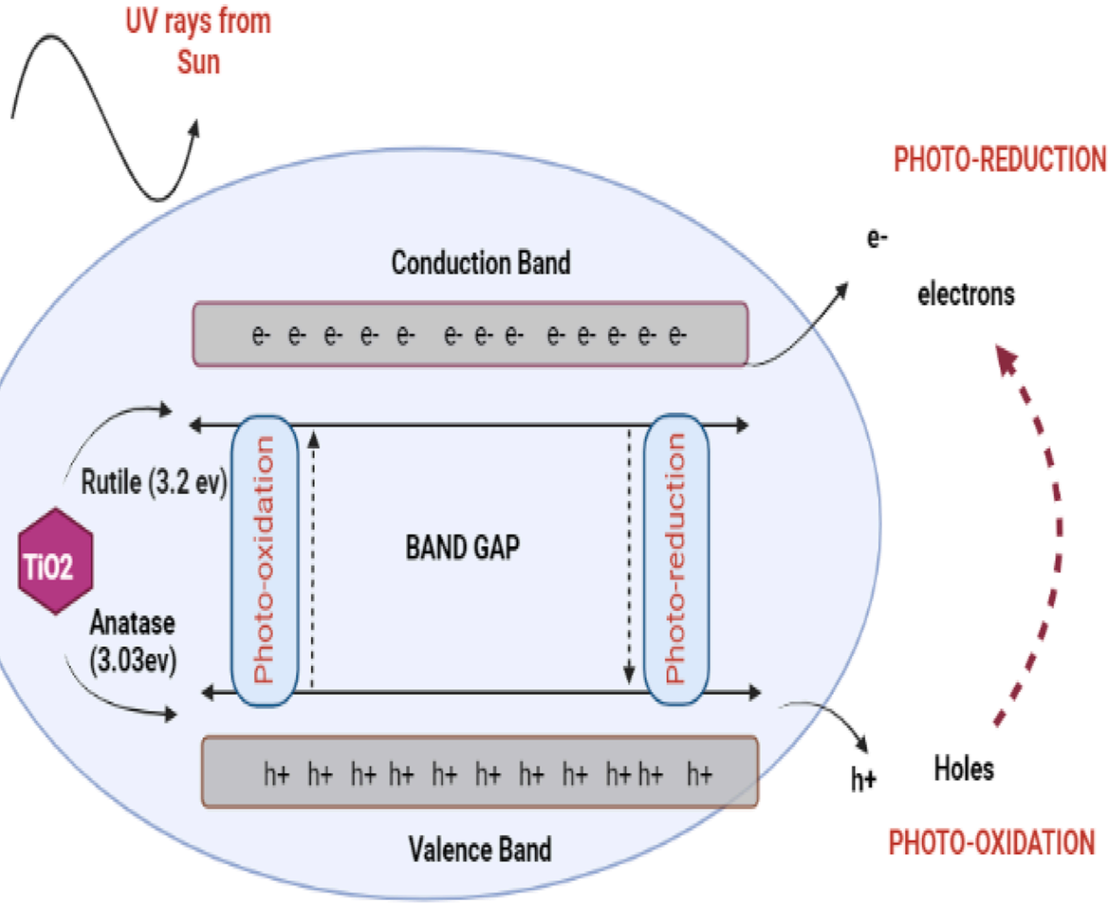

Fig. 5. Series of steps in photo-generated redox reactions.

Table 2
Properties and results of dermal exposure to TiO_2 nanoparticles.

Size	Type of emulsion	Structure	Status of Penetration	References
43 nm	Nano-TiO_2	Crystalline	Yes, skin	[66]
15–40 nm	Nano-TiO_2	Solution	Not known	[41]
38 nm	Nano-TiO_2	Powder	No penetration	[67]
20 nm	Nano-TiO_2 (rutile)	Rod-Shaped	No penetration	[68]
20–30 nm 50–150 nm	Water in Oil emulsion	Needle shaped	No, NPs present in the upper layer of the skin	[69]
10–50 nm	Oil in Water and Water in Oil emulsion	Agglomerates	Minimal penetration in the upper layers	[42]

quite suitable for use as a preservative in cosmetics [88].

In addition, it has been proposed that silver promotes disruption of the bacterial cell wall due to the antibacterial properties of AgNPs. Additionally, Kim et al., 2008, demonstrated that AgNPs suppress the proliferation of dermatophytes. Thus, AgNPs act as anti-infective agents and possess antibacterial and antimicrobial properties [89]. In acne situations, the incorporation of silver nanoparticles in cleansing soaps is very advantageous because of its bactericidal and fungicidal properties [90]. Thus, they can be used in cosmetic products for their preservative effects, particularly in acne formulations. In addition, silver nanoparticles can protect against atopic dermatitis of the skin, but the mechanism associated with this protective effect is not yet clearly known [27]. The fact that the antibacterial properties of AgNPs are achieved at low concentrations, allows their inclusion in cosmetic products with antibacterial effects, particularly in deodorants. Based on several investigations, the liberation of silver ions may contribute to the antimicrobial activity of AgNPs [27]. In addition, they are also used as chemopreventive agents, namely in sunscreens. AgNPs obtained by chemical synthesis are more effective than zinc oxide nanoparticles. The green chemistry of AgNPs with the natural plant extract acts as a reducing agent providing greater sun protection against UV radiation [91]. Including silver nanoparticles in ZnO and TiO2 turns them both small and transparent. This helps them absorb only UV light, excluding the absorption of visible light. Thus, can be used effectively in sunscreens [92,90].

AgNPs are used in the cosmetic industry for their pro-healing effects, namely anti-inflammatory, which contributes particularly to better wound and burn healing. [93,27]. In a nanosilver skin gel, the amount of silver is 30 times less than in silver sulfadiazine, a molecule that is widely used in this context. This is beneficial to treat patients with burnt skin. Thus, AgNPs heal and repair skin tissues [27]. In one study silver nanoparticles were coated with zinc oxide (Ag@ZnO) and found to stimulate the proliferation and migration of human keratinocytes (HaCaT). This led to increased expression of Ki67 and vinculin (a membrane cytoskeleton protein) at the anterior border of the wounds. Remarkably, Ag@ZnO stimulated the production of antimicrobial peptides hβD2 (human beta-defensin 2) and RNase7 by keratinocytes. This promoted antibacterial efficacy against extracellular and intracellular *Staphylococcus aureus* isolated from wounds [94]. Regarding the penetration studies it was found that the penetration of AgNPs depended on the type of cosmetic and the exposure time on the membrane. Additionally, when AgNPs were formulated with hydrogel masks, the viscosity of cosmetic products affected their penetration. This formulation (possessing higher viscosity) caused deeper penetration of AgNPs [93]. Furthermore, it was also found through a stability test that silver nanoparticles can preserve the cosmetic even after a period of 7 months [93]. In bacteria, the AgNPs attach themselves to the cell membrane and reach the interior of the bacteria as well. The AgNPs primarily target the respiratory chain and then interfere in the cell division process, and finally in cell necrosis. The bactericidal activity is enhanced by the release of silver ions into the bacterial cells. Thus, AgNPs kill bacteria by disrupting the cell wall. AgNPs display antibacterial effects on *Escherichia coli*, *Bacillus subtilis*, *Vibrio cholera*, *Pseudomonas aeruginosa,* and *S. aureus* [27].

The antifungal effect attributed to AgNPs derives from the damage caused by the free radicals derived from the surface of the silver nanoparticles on the cells [89,27,93]. AgNPs showed relevant antifungal properties against *Trichophyton mentagrophytes* and Candida spp. (like *C. tropicolis*, *C. parapsilosis*, *C. albicans*, *C. glabrata,* and *C. krusei*) [89]. Thus, it facilitates the treatment of acne and seborrhoeic dermatitis [93]. In addition, it has been discovered that AgNPs can eliminate yeasts like *Candida glabrata* and *Candida albicans* which are responsible for many mouth infections; as AgNPs kill these yeasts, so AgNPs can be combined in dentifrices [95].

It is important to note that the antimicrobial effectiveness of silver nanoparticles is associated with the size of these nanoparticles. A smaller particle size implies a higher surface area to volume ratio, which is associated with a greater antibacterial effect [96]. Thus, the lower the particle size, the more effective they become [27]. Studies also show that AgNPs with a size below 30 nm are very rigid and can passively penetrate the skin, reaching the deeper layers of the SC and the outer surface of the epidermis [93]. On the other hand, the smaller AgNPs have also shown toxicity in various animal models as well as in human cell lines. It has been found that depending on the size, shape and type of carrier AgNPs exhibit different physical and chemical properties [47]. Thus, the concentration and especially, the size of silver nanoparticles must be taken into consideration.

2.5. Gold nanoparticles

Gold nanoparticles can be used in a diversity of shapes and sizes to provide various functional changes, depending on the purpose. The size is typically between 5 and 400 nm, and the shapes used are nanocubes, nanospheres, nanorods, nanosheets, nanoshells, and nanotriangles, among others [97]. It is widely used in cosmetics for wound healing, antimicrobial, drug delivery, and skin tissue regeneration [98,10,99]. The reason for these applications is that they possess a broad range of characteristics and properties. AuNPs are inert, less toxic, biocompatible, have good skin penetration ability, and drug loading capacity, and can be easily conjugated and modified [1,2,99], improve blood circulation, antibacterial and antiseptic properties, enhance skin firmness, have anti-aging and anti-inflammatory properties, and contribute to the skin nourishment [100,12,101].

When gold nanoparticles were combined with silver nanoparticles in different ratios, they produced a wide range of colors, and the color formed was also stable for a long time. The patent for this innovation is held by the Korea Research Institute of Bioscience and Biotechnology. Therefore, they have been used in lip care products such as lipsticks and lip gloss [102]. Similarly, because of their excellent anti-microbial properties, AuNPs are commonly used in deodorants and body sprays alongside AgNPs. This, combined with its low toxicity and inertness, allows it to be used in commercialized toothpastes and mouth fresheners [73]. Although AuNPs have been shown to have antibacterial activity, they were only found to be effective against gram-positive and gram-negative bacteria [103].

Walter et al. developed a technique for producing AuNPs within the central core cortex of human hair. According to the procedure, white hairs were soaked in a gold solution, which initially turned the hair yellow before turning brown over time. The team also discovered that this method of hair dyeing was more long-lasting [104].

Whitening and anti-inflammatory properties were discovered in biogenically synthesized formulations of arbutin-gold nano complexes. Here, the best-performing formulation (GNP-P2) was formed by initial reduction using phenyl β-D-glucoside. Then, phenyl β-D-glucoside-GNP pellets were washed with arbutin. Generally, glucosides have been reported to inhibit melanogenesis, but here when arbutin and phenyl β-D-glucoside were treated against B16F0 melanoma cells, their inhibition levels were less than that of the GNP-P2 formulation attesting that synergistic effect enhances the whitening ability. Further, they were also only 10 nm in size and exhibited no *in vivo* toxicity [52]. Jiménez-Perez and his colleagues created AuNP spheres ranging in size from 10 to 20 nm from Panax Ginseng. According to the moisture retention tests, this ecofriendly synthesized AuNPs (developed by a method using fresh P. ginseng leaves, previously described by Singh et al. [105]) and had a maximum moisture retention capacity of approximately 75.6 percent, which was close to 79.7 percent of the control glycerine, which is extensively used in marketed cosmetic products as a hygroscopic and humectant ingredient. It was also discovered that the whitening effect of the produced AuNPs was caused by decreased mRNA levels of melanogenesis-associated transcription factor and tyrosinase enzyme, thereby validating AuNPs' multifunctional ability in cosmetics [51]. Haddada et al. subjected human skin cells to UVA radiation and discovered an 8-fold increase in MMP-1 levels, which were significantly reduced by treatment with green synthesized AuNP (obtained through plants originated from natural habitats in Reunion Island and without the use of organic solvents for extraction, a green method previously described by Morel et al. [106]), which also prevented the production of oxidized proteins, demonstrating antioxidant abilities. Further research by the team revealed that AuNPs are non-sensitizers and non-irritants, implying that they could be considered for scaling if successful *in vivo* [50]. AuNPs synthesized from Woodfordia Fruticosa with sizes ranging from 10 to 20 nm demonstrated wound healing and microbial adhesion *in vivo*. The rejuvenation of the epithelial lining, the aggregation of collagen fibrils, and the formation of granular tissue resulted in wound closure and healing that was comparable to that of the marketed drug, 5 % Povidone Iodine [107]. Gubitosa and colleagues used snail mucus as a reducing agent for gold and then conjugated itself over the formed AuNPs in their studies. The scratch tests revealed that AuNPs can heal wounds. It was discovered that AuNPs with the highest concentrations resulted in approximately 50 % faster-wound closure compared to the control at the end of two days without affecting cell viability [49]. Calreticulin-functionalized gold nanocomposites have been shown to improve fibroblast migration and promote clonogenicity in keratinocytes and fibroblasts [108]. Lee et al. prepared two phyto-AuNPs, gallic acid-isoflavone coated AuNPs (GI-AuNPs) and protocatechuic acid-isoflavone coated AuNPs (PI-AuNPs), to investigate their role in wound and surgical healing. According to the findings, there is no size or shape effect on skin regeneration. The nanoparticles successfully enhanced skin regeneration and healing in animal models by directly or indirectly increasing the levels of TGF-1, VEGF, collagen, keratinocytes, Ang-2, and granulation tissues [109].

In terms of inorganic nanoparticles' presence in the cosmetics market, AuNPs have a significant share. Cosmetics maker Chantecaille has come up with Chantecaille Nano Gold Energizing Cream and Nano Gold Energizing Eye Serum. The AuNPs in these products were found to have collagen stimulation and cell regeneration abilities and also were further enhancing the skin by providing glow and preventing skin wrinkling contributing to anti-aging. Another cosmetics manufacturer, LR Zeitgard, has developed LR Nano Gold Day & Silk Day Cream a product that protects against UV rays, preventing premature aging of the skin caused by interaction with light [110,111,112,27,99,113]. Nanorama, a nano gold mask pack was produced by Lexon Nanotech. This face mask acts as a disinfectant and also reduces pores in the skin, helping in the treatment of acne [104]. This list of AuNP-containing products doesn't end here. There are more products available in various forms with varied benefits [110,111].

2.6. Copper nanoparticles

Copper is one of the few elements that can be found naturally on the planet. It is also less expensive due to its widespread availability. Copper's use in cosmetics dates back to 1550 BCE when its wound-healing ability was mentioned in the Ebers Papyrus [114]. Because of its multifaceted role in anti-aging, coloring, wound healing, and hair care, copper has been used in cosmetics [115]. Aside from these effects, they have anti-microbial, anti-oxidative, and anti-cancer properties, making them excellent cosmeceutical.

Copper tripeptide formulations are part of several cosmetic products already on the market, including skin creams. Its ability to remove the extracellular matrix's sun-damaged proteins, collagen, and elastin promotes faster wound healing. It also protects against protein rupture by activating anti-proteinases, playing a dual role of both prevention and cure, depending on the situation [116].

Copper nanoparticles (CuNPs) ability to act as a colorant has long been used in color glasses [117], and it is now being applied to cosmetics (European Chemicals Agency (ECHA)). CuNPs are FDA-approved for external cosmetic use, including the eye. CuNPs are used as a colorant in the CoverGirl Liquiline Blast Eyeliner Pencil, which is proof of this (Consumer Product Information Database- USA).

The small size and high surface/volume ratio of CuNPs allow them to interact closely with microbial membranes, promoting a high antifungal/antibacterial capacity [118]. In addition, in solution, there is a facilitated release of its ions, which promotes the formation of free radicals. The lipids in the cell membranes are then destroyed by oxidation, compromising all the biochemical processes that are fundamental to cell viability [119]. The smaller the size of the CuNPs, the penetration of CuNPs through the skin increases, causing damage to the liver, kidney, and spleen [120]. For this reason, even today, the use of CuNPs in cosmetics is lower [121] than that of its other metal counterparts, namely gold and silver.

2.7. Aluminum oxide nanoparticles

Al_2O_3 nanoparticles are primarily used as coating agents in TiO_2 and ZnO formulations, where photocatalytic activity causes an increase in ROS, thus increasing oxidative stress. In these cases, alumina, aluminum hydroxide, or silica nanoparticles are typically coated to increase TiO_2 dispersion, improve formulation compatibility, avoid direct contact of TiO_2 over the skin, thereby increasing safety, and finally reducing photocatalytic activity, which some studies suggest is not highly efficient [122].

Al_2O_3 nanoparticles are well known for their soft-focus effects, which aid in the concealment of skin irregularities. This has led to a variety of market products, such as concealers, face powders, and foundations [123,3]. Revlon's Colorstay Stay Natural Powder and New Complexion concealers are two products that contain nano-alumina as an active ingredient [73]. Because its base formulation contains nano-sized aluminum flakes, Timicron Glam Silver emits a halo effect on the surface to which it is applied. These flakes are responsible for the silvery-white pigments that give the glow [124].

Alumina nanoparticles' cosmetic application extends beyond skin care. It is used in tooth polishing and remineralization [6]. To control frizzy hair, the composition included hydrophobically surface-modified aluminum oxide nanoparticles, silicone fluid, and silicone acrylate film former [125].

2.8. Nanocrystals

Nanocrystals are aggregated atom clusters in either a single or polycrystalline arrangement that, when dispersed in water, form topical formulations, or nanosuspensions [126,113]. The particle sizes range from 100 nm to 400 nm. According to current European cosmetics regulations, they are not considered nano because their size is greater than 100 nm, they are highly water-soluble, and they can biodegrade [127]. They are mainly used for compounds with low aqueous solubility. Top-down and bottom-up approaches are employed to create them. The top-down approach is based on high-pressure homogenization and wet ball milling and is considered the most advantageous [111].

Nanocrystals are preferred over other nano forms in cosmetics due to their improved solubility and adhesiveness, which increases retention rate and thus bioavailability and bioactivity [110]. Due to these properties of nanocrystals, a slew of nanocrystal-based cosmetic products was introduced into the market: Juvedical, a rutin-based nanocrystal, was the first commercially marketed nanocrystal product in 2000 by Juvena using smartCrystalsTM technology [57]; Platinum Rare by La Prairie, a hesperidin-based nanocrystal [128]; Renergie Microlift by Lancome [113], a ZnO nanocrystal-based moisturizing cream Nano-In Hand and Nail Moisturizing Serum, and Foot Moisturizing Serum developed by Nano-Infinity Nanotech [129], in which Zn^+ ions play an important role in modifying the matrix metalloproteinases behavior contributing for skin maintenance [58]. Liu Zhaoping and colleagues also created Silybin nanocrystals with anti-wrinkle and skin-tendering properties [130]. Here nanocrystals enhance bioavailability while silybin's protective effect against UV-B rays and anti-oxidant properties give the anti-aging characteristics [131].

When compared to unmodified rutin and chemically modified rutin glycoside, rutin nanocrystals were found to be highly efficient. At a concentration of only 0.01 %, the rutin nanocrystal had 160 % higher UV absorption and twice the bioactivity in comparison to the unmodified rutin concentration, which was 500 times higher. Compared to chemically modified rutin glycoside, it showed 1000 times higher bioactivity [120]. Stansic et al. used various methods to create hesperidin nanocrystals with particle sizes ranging from 100 nm to 500 nm. This was then developed into an oil-in-water silky cream and tested on an artificial skin model. The results showed that the best formulation had no toxic effects. It has also been shown to reduce dark circles under the eyes, have skin-whitening effects with regular use, and prevent irritation caused by UV exposure. The major mechanisms by which these effects were brought upon by hesperidin are its chelation abilities that in turn inhibit enzymes like tyrosinase, and elastase, among others, and by blocking melanophilin which helps in depigmentation. Also, similar to nanocrystals, hesperidin helps in increasing bioavailability by improving epidermal penetration [59].

Symurban is an antagonist of the Aryl hydrocarbon receptor (AhR). When exposed to air pollution, AhR is activated in the skin, causing an increase in matrix metalloproteinases and pro-inflammatory cytokines. Taking this into consideration, Kopke et al. created symurban nanocrystals that improved skin penetration and thus provided better protection against harmful environmental effects [56].

Apigenin, a flavonoid noted for its antioxidant, anti-inflammatory, and anti-allergic properties, was prepared using second-generation smartCrystal technology known as Combination technology. Apigenin nanocrystals with a size of 400 nm were created. These apigenin nanocrystals produced similar sun protection factor results *in vitro* as rutin nanocrystals did *in vivo*, indicating their potential as a UV-protective anti-aging cosmetic product. Though they are due to the antioxidant properties of apigenin the macro suspensions of apigenin showed an EC50 value twice that of the apigenin nanocrystal formulation stating its low antioxidant ability. The team checked the saturated solubility of both macro and nanosuspensions and found those to be 1072 μg/ml and 1204 μg/ml which isn't a significant reason for the higher DPPH activity of nanocrystals. So, it was inferred that the increased surface area and high saturated solubility in methanol were the reasons why nanocrystals promoted apigenin's antioxidant properties [58].

According to Lidan Xiong and colleagues, anthocyanin-encapsulated cellulose nanocrystals in lipstick and lip gloss are more efficient and safer. They show high protection rates with a 10-fold higher sun protection factor value after incorporating cellulose nanocrystals with anthocyanin. These particles improve anthocyanin's anti-UVB function, protect against DNA damage, have good bioadhesion, are water-resistant, and can be easily wiped with a wet towel [132].

Aside from the ones listed below, numerous other chemical compounds have been formulated into nanocrystals, particularly flavonoids due to their low water solubility. Among them are lutein, glycyrrhetinic acid, resveratrol, caffeine, and others. These nanocrystals are used in both cosmetic and cosmeceutical applications. Mitri et al. [33] created lutein nanocrystals with sizes less than 500 nm that have good UV radiation protection as they can block high-energy photons (blue light) and scavenge the free radical species after lipid peroxidation. Resveratrol has also been used in various cosmetic products, including liquid, gel, cream, lotion, and so on. This is primarily due to its skin-brightening ability, skin repair and regeneration role, and anti-aging and anti-wrinkle enhancement ability caused by its excellent antioxidant properties. However, it suffers from low thermostability issues. To improve its efficiency, Kobierski et al. [133] created resveratrol nanocrystals with sizes ranging from 150 to 200 nm as nanocrystals have increased saturated solubility and dissolution velocity. In the normal human body, the coenzymes start to deplete in the early thirties reducing the collagen and elastin production in the skin. Coenzyme Q10 which is considered to be the "biomarker of aging" can be supplemented to avoid deterioration due to aging. But, this faces the issue of solubility and so Coenzyme Q10 has been developed into a nanocrystal form, providing improved sun protection benefits by acting against UV rays, inhibiting photoaging and premature aging [33].

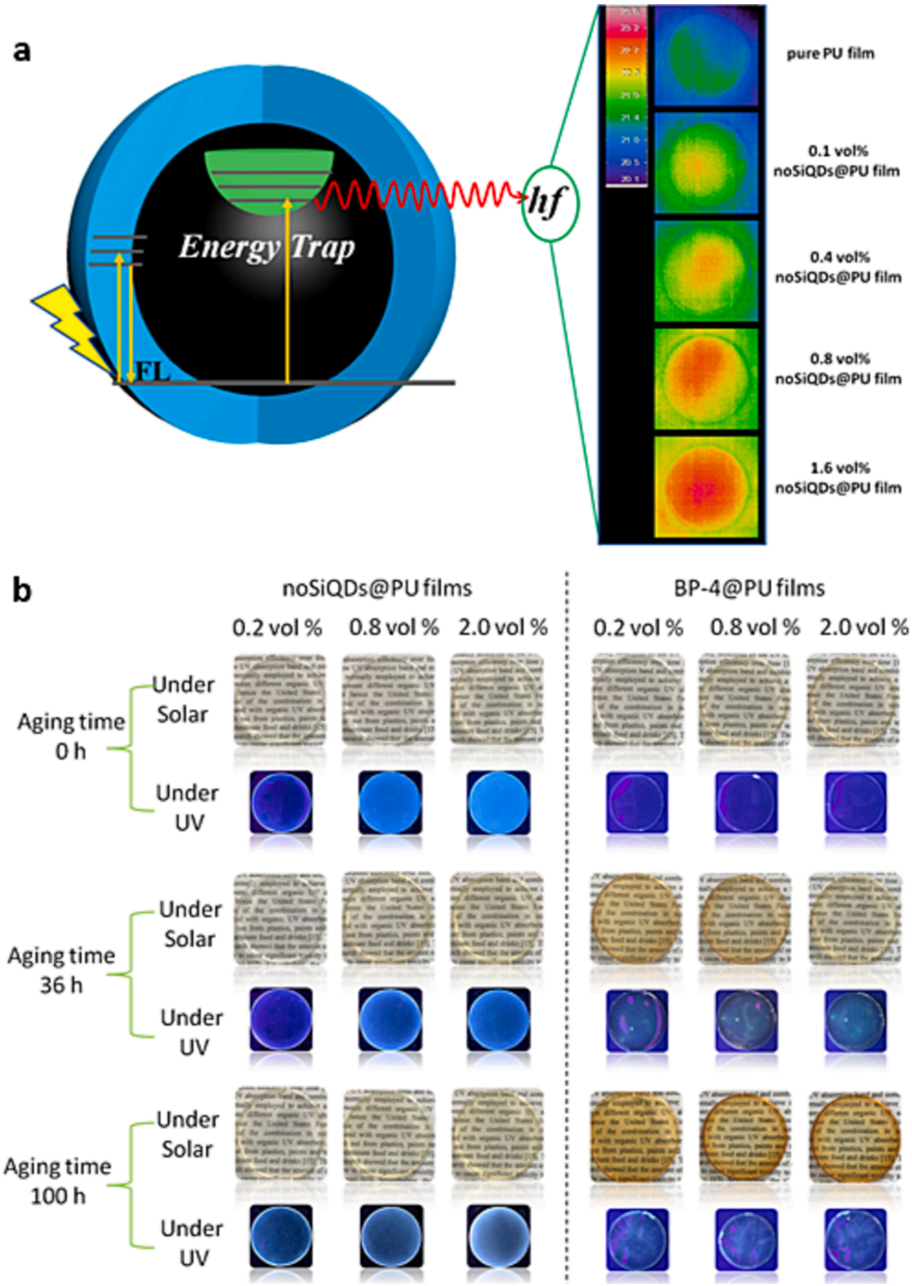

Fig. 6. a) Illustrative image of the mechanism of UV absorption by noSiQDs (left) and infrared images showing Polyurethane (PU) films with different concentrations of fluorescence-quenched noSiQDs (right); b) Yellowing and corresponding fluorescence of the noSiQDs@PU films with three concentrations of noSiQDs under radiation from a xenon lamp with a power of 6000 W for 0, 36 and 100 h (left). The same treatments and measurements of BP-4@PU films with the same concentrations of BP-4 were performed (right) [60].

2.9. Quantum dots

Quantum dots are particles with sizes ranging from 1 nm to 10 nm. They have distinct optical and magnetic properties. Because excitons (analogous to electrons in atoms) can be excited to higher energy levels where UV absorption occurs and emission occurs while returning to the ground state, quantum dots are thought to be analogous to atoms. As a result, these semiconductor quantum dots that oscillate between the valence and conduction bands are also known as artificial atoms.

The Greeks and Romans created the first documented instance of quantum dot synthesis for cosmetics over 2000 years ago when they created PbS quantum dots for hair dyeing using PbO, water, $Ca(OH)_2$, and other ingredients [134]. Neon nail polishes are now commercially available. This neon color is created by stimulating quantum dots, which emit fluorescence in the UV–visible range. Commercially available neon nail polishes include Neon Color Trend Avon and Neon Milani Nail lacquer [124].

Guangqi Hu et al. created a silicon quantum dot-based UV absorber system (Fig. 6 a) to address issues such as low transparency, low absorption efficiency, and high toxicity. In this system, silicon quantum dots (SiQDs) were functionalized with OH and NH functional groups (noSiQDs) to form particles with sizes ranging from 4 to 6 nm. Their UV absorption was compared to commercially available Benzophenone-4 (BP4)-based sunscreen cosmetics, and the results demonstrated that noSiQDs outperformed BP4-based sunscreen cosmetics in terms of anti-yellowing efficacy (Fig. 6b). This was due to the noSiQDs' full-band UV absorption and high UV absorption efficiency. The noSiQDs blocked 98.83 percent of UV rays at a concentration of 2.0 vol% and had an SPF of more than 50 [60].

Asok et al. developed an effective method for converting UVA emission from ZnO nanoparticle sunscreens using defect-rich ZnO quantum dots. UVA emission is undesirable in the cosmetics industry because it increases the production of ROS, which leads to a variety of skin diseases. To address this, sunscreen formulations containing defect-rich ZnO with broad green fluorescence were developed, as an increase in the elements responsible for green fluorescence reduces harmful UV exposure and aging. To confirm this, the researchers examined the fluorescence levels in control ZnO (C-ZnO) and defect ZnO (D-ZnO) on the surface of a skin emission model. The obtained results, bluish violet for C-ZnO and yellowish-green for D-ZnO, represented the ability of D-ZnO's to provide increased green fluorescence. The UVA and visible emission levels (Fig. 7b, 7 d) were then measured in both C-ZnO and D-ZnO coated skin emission model surfaces. The UVA to visible emission ratio was found to be 0.35 for C-ZnO and 0.071 for D-ZnO, indicating that the emission in the visible region is greater (Fig. 7a, 7c). As a result, the D-ZnO formulation can be used not only as a sunscreen but also to

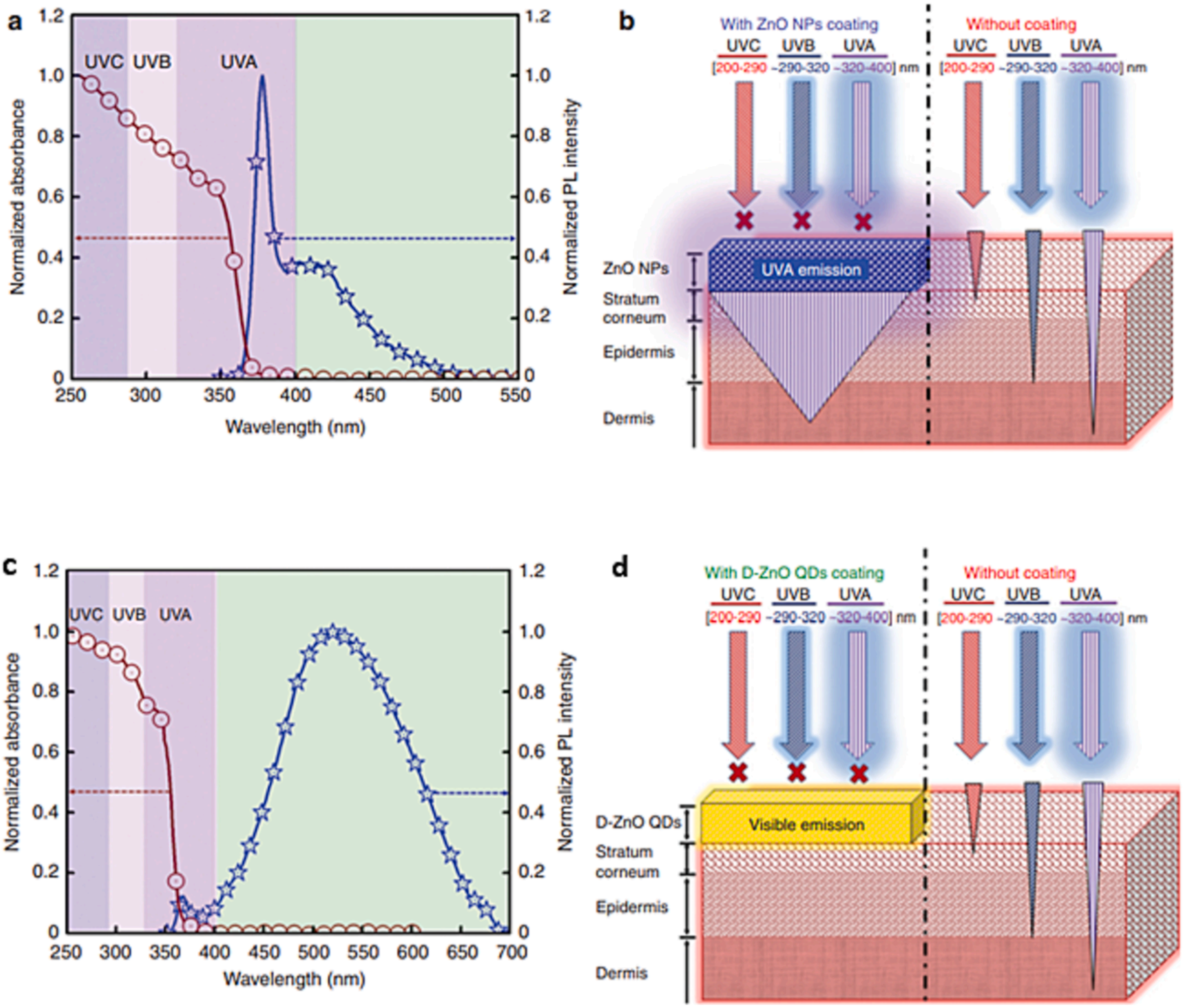

Fig. 7. (a,c) Absorption and emission spectra of C-ZnO & D-ZnO NPs, respectively; (b,d) Penetration of intense UVA emission from C-ZnO & D-ZnO NPs, respectively, to the dermis (left side of both images) and penetration of UVC, UVB, and UVA without sunscreen (right side of both images) [34].

maintain a youthful appearance. It can also be used to camouflage skin color due to the visible defect luminescence [34].

3. Safety and regulatory concerns

A study conducted by Samberg et al., (2010) evaluated the cytotoxicity potential of AgNPs *in vitro* using human epidermal keratinocytes (HEKs) and *in vivo* evaluated their inflammatory effect and penetration ability in pig skin. The macroscopic observations in the study did not show any irritation in pig skin, although areas of focal inflammation and the presence of AgNPS were found on the skin surface, particularly in the upper areas of the SC, using microscopic and ultrastructural observations. Regarding cytotoxicity, this study shows that HEKs are affected by residual contaminants in AgNPs solutions and not by AgNPS themselves, showing that they are not responsible for cell death since when used in washed or carbon-coated solutions toxicity does not occur [135].

In a study in animal models (*in vivo*) and cell lines (*in vitro*), the effectiveness of the protective effect of AgNPs against UVB was examined. The results obtained showed that AgNPs attenuated the effect of UVB damage on both keratinocytes and the skin of animal models. Additionally, this protective effect was found to be equivalent to that conferred by nano-sized rutile TiO_2NPs. This study shows that AgNPs are efficient and safe as active ingredients for sunscreens, namely for protection against UVB-induced skin damage [46]. Another study evaluated the toxic potential of 15 nm AgNPS coated with polyvinylpyrrolidone *in vitro* in primary normal human epidermal keratinocytes (NHEK), where different concentrations of AgNPs were used. This study showed for the first time that AgNPs may present some toxic potential for primary keratinocytes, given the activation of genotoxic and cytotoxic processes depending on the AgNPs concentrations. These processes include decreased cell viability of keratinocytes, metabolism and proliferation/migration of these cells, activation of caspase 3/7, and the presence of DNA damage [47]. As per the Safety Data Sheet (ACS material LLC), the ecological data of AgNP is as follows: "Toxicity: data is not available; bioaccumulative potential: data is not available; mobility in soil: data is not available; results of PBT and vPvB assessment: this substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1 % or higher. For the other adverse effects, there is no data available. For the waste treatment methods: a licensed professional waste disposal service must be contacted to dispose of this [136]".

Skincare products are also using, TiO_2 and ZnO nanoparticles extensively, so there exists ambiguity regarding their safety profile upon interaction with the skin cells. *In vivo,* studies show that prolonged exposure to these nanoparticles causes pathological lesions, alteration in morphology, and free radical production, leading to systemic response, and continuous exposure causes decreased mitochondrial functionality by changing its size and fighting with free radical capacity [137]. But, a ray of hope exists as these toxicity effects can be drastically reduced by coating them with biocompatible fatty acids like palmitoleic, oleic acids, etc which has been shown by a study done on fibroblast and adenocarcinoma cells, where penetration power and cytotoxicity was markedly declined in contrast to bare naked used of TiO_2 and ZnO particles [138]. This strategy could be utilized by the cosmetic industry for its better applicability.

There have been quite a good amount of studies of SNPs toxicity (*in vivo* and *in vitro*) utilized for cosmetics. SNPs exposure has been studied profoundly in Kupffer cells leading to liver cell damage. This damage activates the NF-ķß pathway (signaling), which leads to endothelial damage through the autophagy process [139]. Different sizes of nanoparticles (SNPs) ranging from 42 to 291 nm with different functional groups were examined in skin cells. It was found that although the formation of agglomerates compromises cell absorption, particle size is the most limiting factor. It was also found that the positive functionalization of the particles contributed to their cellular absorption *in vitro*. Functionalizing positively charged groups is important for the *in vitro* uptake of the particles, however, aggregation is a limiting problem. When tested *ex-vivo*, only particles with a size of around 42 nm were associated with epidermal cells, regardless of surface functionalization [140]. Hair products use SNPs of a specific size range between 400 and 700 nm because this size is required to achieve product penetration (cosmetics) inside the hair follicles [45]. Additionally, studies are showing that amorphous SNPs with sizes between 30 and 1000 nms can activate immune effects and some allergic diseases. According to a cytotoxicity study, weakly negative charged SNPs with exact sizes of 20 and 100 nm, showed higher toxicity than higher charged NPs. A size of 70 nm was able to induce an elevated ROS, causing DNA damage to (human) keratinocyte cell lines [141]. The utilization of SNPs can enhance the physicochemical stability of the drugs that are labile in nature, which promotes release in the skin and its penetration. There are still gaps in understanding the potential risk of using SNPs to both humans and the environment, their fate in interfering with geochemical cycles in the environment, and their behavior in the body. These parameters have to be checked to make it a suitable drug carrier/agent.

AuNPs of size 1–10 nm have passed the skin barrier through the small pores in the skin and have accumulated in large quantities in the epidermis and dermis [142]. According to Filon et al., the penetration of AuNPs from the outermost surface of healthy skin was significantly higher compared to damaged skin [143]. Qiu et al. evaluated the skin penetration of AuNPs synthesized from plants. The team examined various parameters influencing skin penetration and discovered that skin penetration occurred in the following order: SC > epidermis > dermis. Furthermore, citrate-stabilized hydrophilic AuNPs did not penetrate the inner layers. It was proposed that hydrophobic green synthesized AuNPS could penetrate even the deepest layers of the skin [144]. However, small AuNPs (22 nm) penetrated the thick skin much more effectively than larger AuNPs (105 nm and 186 nm). Raju et al. performed a histological analysis of the penetration of AuNPs revealing no toxicity in tissues below the SC but did circulate in the blood [145]. Various groups have worked on AuNPs to understand their toxicity and their potential in cosmetics. Though there are studies that support the safety of AuNPs, the results presented by a few groups are equally contrasting. This has primarily concerned the dose concentration and nanoparticle size [146,147]. AuNPs were extracted from four commercially available gold-based cosmetic creams by Cao et al. To determine the toxicity levels, the creams with the highest extracted gold content were subjected to cell viability and PI staining tests. Because the gold in these creams was in the form of gold nanosheets, there was no toxicity even at high doses and 24-hour exposure because the Au nanosheets were only on the surface of keratinocytes [148]. In a subsequent study, the team discovered that permeation occurs through hair follicles and affects hair growth (Fig. 8 a). As gold nanosheets are barely absorbed into the systemic circulation, there was an insignificant decrease in cell viability of keratinocytes and fibroblasts' toxicity (Fig. 8b) [48]. Despite numerous studies supporting the safety of AuNPs, Ramanunny et al. (2021) linked AuNPs to noxiousness and scaling-up issues to particle sizes between 1 and 100 nm [149]. When exposed to AuNPs of 13.5 nm size, mice models showed decreased body weight, RBC count, and spleen index values [150]. Pernodet et al. produced 4 nm AuNPs modified with citrate. These particles penetrated the membrane, killing dermal fibroblasts [151].

Alizadeh et al. found that following 21 days of CuNPs exposure, the wounds were almost completely healed, revascularized, and no toxicity was observed [152]. *In vitro* studies by Bengalli et al. show that when CuNPs in antimicrobial textiles were exposed to acidic sweat, they released Cu + ions. This was discovered to be toxic to the epidermis rather than the NPs themselves [153]. According to Luo et al. and Alarifi et al. [154], a significant reduction in cell viability is seen in HaCaT cells after treatment with copper oxide nanoparticles (CuONPs), whereas Andreani et al. [155] present that CuONPs dispersed in water do not reduce cell viability in HaCaT cells.

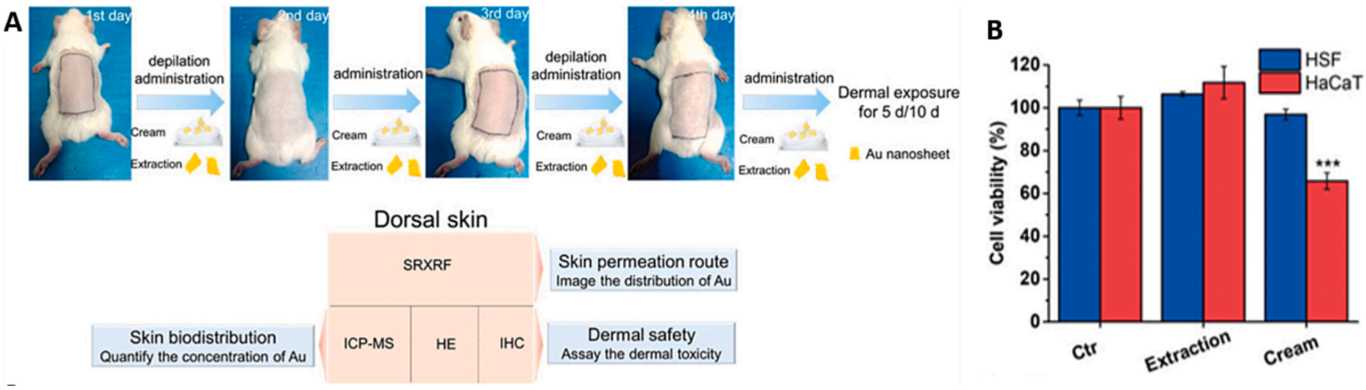

Fig. 8. a) Schematic illustration of 5d and 10 d dermal exposure to a cream formulation and an extracted Au nanosheets for the evaluation of skin permeation, biodistribution, and dermal safety (*in vivo*); b) Cell viability after continuous application for 5 days of the cosmetic cream and Au nanosheets extracted for HSF (Human Splenic Fibroblasts) and HaCaT [48].

Mauro et al. investigated the transdermal absorption of alumina nanoparticles with diameters ranging from 30 to 60 nm. These NPs were tested against human skin excised synthetic sweat, and the skin permeation levels for damaged skin were 0.0028 percent and 0.0011 percent for intact skin. This strongly suggests that alumina nanoparticles are safe because the Al inherent in these 0.0028 % and 0.0011 %, is considered to be traceable to the human body [156]. Another study on the effect of alumina nanosheets and nanofibers on L929 cells discovered that treatment causes lower cell viability as well as sluggish cell proliferation, but the levels of reduction and sluggishness are not high enough to hurt the system [157]. Balakrishnan et al. recently investigated the wound-healing ability of alumina-polyvinylpyrrolidone nanofibrous scaffolds *in vivo*. The scaffold designed, after 10 days of treatment showed excellent wound healing abilities. The wound healing levels were roughly twofold (80 %) higher than the control (40 %) with even hair growth back on the skin. Furthermore, the skin irritation test reveals that the scaffold had no irritant effects on the animal and was, therefore, safe [158].

Studies have shown that quantum dots with surface coatings and intradermal functionalities are lethal for fibroblasts and keratinocytes. They can also change the levels of protein and gene expression [99]. The toxicity of nanocrystals usually depends on the size and compound, but when compared with other nanostructures of the same size and compound, the nanocrystal's toxicity is low. A study by Nan Ma et al. also validated the low toxicity of nanocrystals as the DNA-passivated CdS nanocrystals had cell viability consistently above 80 % in all their study cases. The dermal and oral toxicity studies on cellulose nanocrystals (CNC) have revealed nanocrystals to be safe and don't cause any health issues. One such study using CNC also achieved a 0 in the Primary irritation index meaning CNCs are non-irritating.

In view of the above, nanotoxicology has gained great importance in order to provide safety data on nanomaterials, and also to allow advances in the area of nanomedicine [159]. The physicochemical properties of nanoparticles, namely their small size and correspondingly large specific surface area, give them specific characteristics. As the particle size decreases, the ratio of surface area to total atoms or molecules increases. This increase makes them good catalysts for chemical reactions, giving them greater biological activity. However, this greater biological activity can be advantageous or not, depending on the effect exerted. For this reason, nanoparticles have to be studied on a case-by-case basis. In addition to particle size, many factors must be taken into account, namely the route of administration and the type of material, which can also influence the results observed in nanotoxicity studies [159].

Nanoparticles utilization and exposure are often regulated by Organisation for Economic Cooperation and Development (OECD) guidelines. It is known that exposure to NPs can be mainly through dermal contact (in textiles, for example), ingestion in food, or by inhalation into the air. In ingestion, due to the acidic stomach environment, AgNPs can convert to their ionic form in the stomach and thus more easily reach the bloodstream. This can cause argyria, intestinal ulcers, and liver damage. Moreover, AgNPs can be deposited in the kidneys, testicles, and brain (crossing the blood–brain barrier) [160]. By inhalation, AgNPs may accumulate in the nasal cavities, pulmonary lymph nodes, and the alveolar region of the lungs. This activates alveolar macrophages which release ROS and induce an inflammatory response. It is also assumed that AgNPs may exhibit toxic and harmful effects in case of short/long-term exposure either in humans or in the environment, caused by their oxidizing and inflammatory capabilities [160]. Furthermore, it is thought that due to their surface area and energetic reactivity, once in the environment, AgNPs may also be subject to different transformations such as oxidation or reduction, sedimentation, and agglomeration that may change their behavior [160].

A key restriction of these NPs is the formation of ROS like hydrogen peroxide (H_2O_2), hydroxyl radicals (OH), or singlet oxygen ($^1O_2$), which can harm a living cell's cellular and genetic integrity, potentially leading to programmed cell death. As a result, to reduce the generation of ROS, these particles should be coated with coating materials or doped with specific elements [161,162]. Also, in the cosmetic field, the primary mechanism for inorganic nanoparticle-induced toxicity is a rise in oxidative stress caused by an increase in the levels of ROS. Nanoparticles have a high risk of negatively impacting the environment, as the NPs used in cosmetics will harm the aquatic ecosystem because these NPs are eliminated along with water in each wash-off, swimming, and so on [163]. The first signs of skin aging result from environmental effects on the skin and also from genetic inheritance. These environmental effects include the individual's lifestyle, climatic conditions, and local pollution levels [111], making it a cyclical process. The application of cosmetics carrying NPs to intact skin has been shown to be safe since a wide range of studies have shown that in these cases the NPs cannot penetrate the deeper layers of the skin. The application of cosmetics containing NPs to intact skin has proven to be safe. However, some recent *in vitro* and *in vivo* studies have shown otherwise, requiring further research to validate the non-toxicity of NPs in the deeper layers, thus ensuring their safety [120].

Cosmetics' biological effects are a major source of concern, as they, like drugs, contact the human body in some way. The presence of nanoparticles increases the possibility of biological changes, whether intended (as in the case of cosmeceuticals) or not. Therefore, in this matter too, regulation becomes essential to ensure the safe use of these products. This gave rise to the EU Regulation 1223/2009/EC (CRP) on cosmetic products, an updated version of the previous Directive 76/768/EC on cosmetic products. The CPR defines a nanomaterial as "an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on a scale ranging from 1 to 100 nm.” Thus, under the current regulation, materials larger than 100 nm in size should not be considered nanomaterials. Furthermore, this does not take into account nano-sized delivery systems, even if their size is between 1 and 100 nm because they will disintegrate further to give out only the molecular components. As a result, in most cases, it refers to active nanomaterials with a size of less than 100 nm.

In the event of a medical emergency caused by cosmetic products, it is critical to understand the ingredients, composition, and other critical details. The Cosmetic Product Notification Portal (CPNP) was created specifically for this purpose. Manufacturers are required to notify the European Commission via CPNP of the product before sales begin. Except for nanomaterials that are pre-approved for use in cosmetic products and are listed in Annex III, a special notification is required 6 months before the product’s marketing, according to Article 16. Next, the Scientific Committee on Consumer Safety (SCCS) will analyze the proposed nanomaterials. SCCS may or may not respond, but the product may be marketed regardless because SCCS is not an approving authority and these do not require approval but regulation. The European Commission has cataloged the overall nanomaterials used in cosmetics, as well as their safety profiles, properties, and functions, and these are available for consumer viewing. Finally, after all, considerations, it was decided that all materials that fall into the “nano” category must be labeled nano within brackets. For instance, gold (Nano) [120]. In 2007, a global organization called the “International Cooperation on Cosmetics Regulation (ICCR)” was formed, which included regulatory authorities from various countries (the United States, the European Union, Japan, Brazil, and Canada) to discuss the safety and regulation of cosmetics [6]. In the United States, regulation of cosmetic products falls under The Federal Food, Drug, and Cosmetic Act. There is also a guide titled “Guidance for Industry: Safety of Nanomaterials in Cosmetic Products” that was published in 2014 to assist manufacturers in making informed decisions about the use of nanomaterials [6].

4. Concluding remarks and future outlook

Because of their properties, functions, and adaptability to specific needs, inorganic nanoparticles are widely used in cosmetics. They allow other compounds to be easily conjugated on their surfaces. This is the main factor that promotes their use in several products, including cosmetics, as they help achieve the desired properties and efficiencies. In particular, the relevance of zinc oxide, titanium dioxide, AgNPs and SNPs in the inclusion of cosmetic products is noted. Zinc oxide and titanium dioxide nanoparticles are broadly employed in cosmetics because of their photocatalytic nature and ability to block UV. These properties are well utilized in sunscreens. The inherent antimicrobial, antifungal, anti-inflammatory, and preservative properties of AgNPs are most relevant for their use in cosmeceutical products. Finally, SNPs have attracted the cosmetic industry because of their hydrophilic nature and low cost. These NPs stand out by favoring the distribution, efficacy, and extending the shelf-life of cosmetic products.

Current toxicity and safety research focuses solely on the route of exposure. In this context, it is important to note that, in general, the toxicity of cosmetics is low or none, according to research studies, because the main route of exposure is through the skin. In addition, this can be further reduced by using more environmentally friendly and sustainable synthesis methods. Still, there is a need for further studies, particularly to clarify the impact of inorganic nanoparticles on other organs of the body (NPs accumulation, systemic toxicity). In addition, information on the long-term effects of these NPs on the human body and the environment is lacking. Besides considering the effects of these nanoparticles on the consumer, it is critical to consider the entire supply chain and all the elements that may be in contact with these nanoparticles at various stages. There should be a thorough understanding of the effects of these nanoparticles on the ecosystem, and care should be taken to eliminate any potential risks that may arise as a result of their presence.

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.

Data availability

No data was used for the research described in the article.

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