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Review Article

Zinc-containing compounds for personal care applications

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Abstract

It is well-known that zinc ions are widely used in cosmetic products. Their popularity is associated with the multifunctional profile of Zn^{2+}, which is classified as an essential chemical element in the human body. This review examines numerous beneficial biological properties of zinc-containing compounds and classifies the compounds used in cosmetic products according to their functionality profile: antioxidant, sunscreen, anti-inflammatory, anti-pigmentation, anti-ageing, anti-acne, antimicrobial, anti-odour, cleansing or stabilizing activity. It also underlines the significance of zinc in enzymatic processes, which depends on the enzyme type acts as inhibitor or enzymatic stimulator. Moreover, the article describes the chemical nature of the most interesting groups of Zn compounds.

Résumé

Il est bien connu que les ions de zinc sont largement utilisés dans les produits cosmétiques. Leur popularité est associée au profil multifonctionnel de Zn^{2+}, qui est classé comme un élément chimique essentiel dans le corps humain. Cette revue examine de nombreuses propriétés biologiques bénéfiques des composés contenant du zinc et classifie les composés utilisés dans les produits cosmétiques en fonction de leur profil fonctionnel: antioxydant, protection solaire, anti-inflammatoire, anti-pigmentation, anti-âge, anti-acné, antimicrobien, anti-odeur, nettoyage ou activité stabilisante. Il souligne également l'importance du zinc dans les processus enzymatiques, qui en fonction du type d'enzyme agit comme un inhibiteur ou un stimulateur enzymatique. De plus, l'article décrit la nature chimique des groupes les plus intéressants de composés de Zn.

General Information about Zn Compounds

Zinc is acknowledged as one of most essential elements in the human body and is classified as a trace element, along with chromium, cobalt, copper, iron, manganese, magnesium, molybdenum and selenium. Zinc is present in various tissues and organs, and it takes part in over 200 chemical reactions regulated by enzymes. The total Zn content in an average human organism is estimated at about 2 g, of which about 60% is present in the muscles, about 30% in the bones and about 6% in the skin [1]. It demonstrates a primary role of Zn^{2+} ions for these external body parts. It is important to note, however, that zinc concentration differs between skin layers, with the amount of Zn in lower dermis estimated to be one-sixth of that in the epidermis layer, so as there is six time less Zn in lower dermis than in epidermis [1,2]. An interesting fact is that although the zinc concentration decreases with age in the epidermis, the same cannot be said for the serum, with no significant difference in Zn serum level observed between middle-aged people (less than 35 years) and the elderly (over 65). This shows that low Zn content in the epidermis may be a consequence of a reduction of local enzymatic activity, and so appropriate cosmetic products containing Zn ions may play an important role in preventing skin ageing.

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In terms of acting as co-factor for various types of enzymes, zinc is similar to magnesium [3]. In enzymatic reactions, zinc typically has a coordination number of 4. This has been observed, for example, in carbonic anhydrase, carboxypeptidase and alcohol dehydrogenase, where the free orbitals of Zn^{2+} are occupied by three histidine nitrogen atoms and one water molecule. Zn^{2+} ions as coordinate covalent bond acceptors are found in many other enzymes and regulatory proteins [3]. The example of the latter is Zn-containing transcription factors, in the form of so-called zinc finger motif. The Zn finger protein family encompasses about 2500 proteins divided into six different classes. The classes are distinguished by the number of histidine and cysteine residues with the proteins [4]. In all of them, Zn^{2+} stabilizes the folded protein structure in a finger-like shape, which can bind to the major groove of DNA double helix.

Total content of zinc in human body depends mainly on dietary intake. The average requirement (AR) values differ in terms of body size and general organism condition. It is considered that sex differences do not affect AR importantly. However, one of the most significant factors to consider, when estimating AR, is the effect of phytate intake-related inhibition on Zn absorption [4]. Despite the presence of zinc in meat, fish, eggs, nuts, dairy products, seafood, legumes and whole grains, as well as many other popular dietary products, it is likely to be poorly absorbed from the food. Zn^{2+} ions interact with other bivalent elements, including calcium, copper and iron, as well as with oxalic acid, phosphates, fibre, tannins and phytates, which are abundant in bran and seeds [1,4,5]. Interestingly, the absorption can be improved by intaking zinc as chelates, for example Zn-bisglycinate [6].

Although food is the main source of zinc, and the best way to prevent deficiency is to follow a correct diet, Zn^{2+} can be administered in numerous types of dietary supplements and even in medicines. Zinc sulphate, gluconate, acetate and asparaginate can be administrated orally; however, far more Zn compounds are used in cosmetics. A wide variety of Zn compounds mirror their multifunctional properties, which depend on the exact nature of anions or chelating agents. The detailed functionality profiles are discussed below.

Chemical nature of Zn compounds

Zn compounds used in skin care products are usually salts, coordinated compounds (complexes) or as the zinc oxide, which is hardly soluble in water.

Thanks to the ability of the Zn^{2+} to accept lone electron pairs, it can be complexed by different ligands. In a complex formation reaction, Zn^{2+} plays the role of a Lewis acid and ligands (L), serve as Lewis bases. The Zn^{2+} typically has a coordination number of 4 or 6:

$$Zn^{2+} + 4 \text{ or } 6L \leftrightarrow [ZnL_4]^{2+} \text{ or } [ZnL_6]^{2+}$$

Depending on the stability constants of the complexes, solutions of the Zn complexes typically possess Zn bound in the form of more or less stable complex, which stays in the equilibrium with a relatively low concentration of Zn ions and free ligands.

Generally, Zn salts possessing ionic bonds have a weakly acidic character when dissolved in water. The Zn ion binds six water molecules, creating a labile complex cation $[Zn(H_2O)_6]^{2+}$ that subsequently undergoes hydrolysis, with the formation of the hydronium ion:

$$Zn^{2+} + 6H_2O \leftrightarrow [Zn(H_2O)_6]^{2+}$$

$$[Zn(H_2O)_6]^{2+} + H_2O \leftrightarrow [Zn(OH)(H_2O)_5]^{+} + H_3O^{+}$$

The pH of the Zn salt solutions depends on the properties of the anions. The stronger is the acid from which the anion is derived from, the more acidic reaction the salt has.

Zinc oxide (ZnO), very often used in topical products, is sparingly soluble in water, with a solubility approximately 2 mg dm^{-3} (20°C). ZnO has an amphoteric nature. Although it is nearly insoluble in water, it will dissolve in strong acids giving Zn^{2+} and in strong alkalis, yielding soluble zincates $[Zn(OH)_4]^{2-}$. In order to improve the water solubility of ZnO, the phenomenon of the so-called salt effect can be applied. This effect bases on adding a substance that has not got common ions with a sparingly soluble compound, to the supersaturated solution of a sparingly soluble compound (herein ZnO). This operation will result in a little rise of ZnO solubility. For example, the presence of a culture medium during the determination of antimicrobial activity of ZnO may increases its solubility according to the mentioned salt effect [7].

The next notable Zn compound belonging to the group of coordination compounds is the Zn–glycine complex. The glycine molecule may be bound with Zn^{2+} in several ways: by one or two oxygen atoms of the carboxylate group or by oxygen and nitrogen atoms forming chelate complexes. The chelating is possible when the glycine does not exist as a zwitterion $NH_3^+–CH_2–COO^-$, but is in its anionic form: $NH_2–CH_2–COO^-$ with a lone electrons pair on the nitrogen atom (Fig. 1) [8].

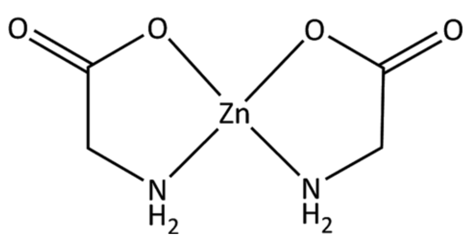

Figure 1 Outline of zinc(II)-glycine complex's structure.

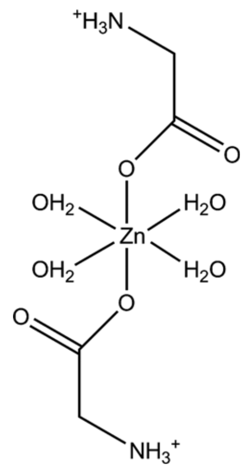

Figure 2 Section of the structure of Zn complex containing glycine.

To give an appropriate example of Zn–glycine complex in which glycine does not play as chelate ligand, a hexaaquazinc tetraaquadiglycinezinc bis(sulphate) of the general formula $[Zn(H_2O)_6][Zn(C_2H_5NO_2)_2(H_2O)_4](SO_4)_2$ was presented (Fig. 2). Conditions in which the complex was synthesized had to promote the existence of the ligand as a zwitterion $^+NH_3–CH_2–COO^-$, and therefore, it coordinated to Zn only by an oxygen atom [9]. Likewise, in the case of another Zn complex $[Zn(Gly)_2I_2]$, the chelate was not formed and glycine adopted a monodentate coordination to the Zn^{2+} (Fig. 3) [10]. When the glycine zwitterion constitutes the ligand, it would also act as a bidentate bridging ligand linked with two Zn^{2+} ions by the carboxylate oxygen atoms [10].

Functionality spectrum of Zn compounds

The wide array of physiological functions of Zn-containing compounds is determined by the chemical nature of the element. Zn is known to control metabolism, growth and development of bones and thus constitutes an essential factor throughout life. It maintains the immune and neuropsychiatric functions and enhances wound healing. It has been observed also that Zn reduces the risk

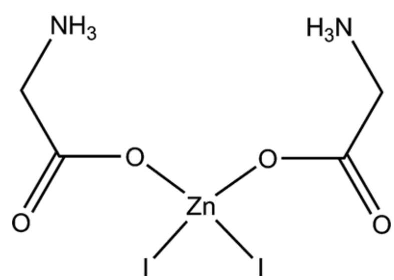

Figure 3 Structure of $[Zn(Gly)_2I_2]$ complex.

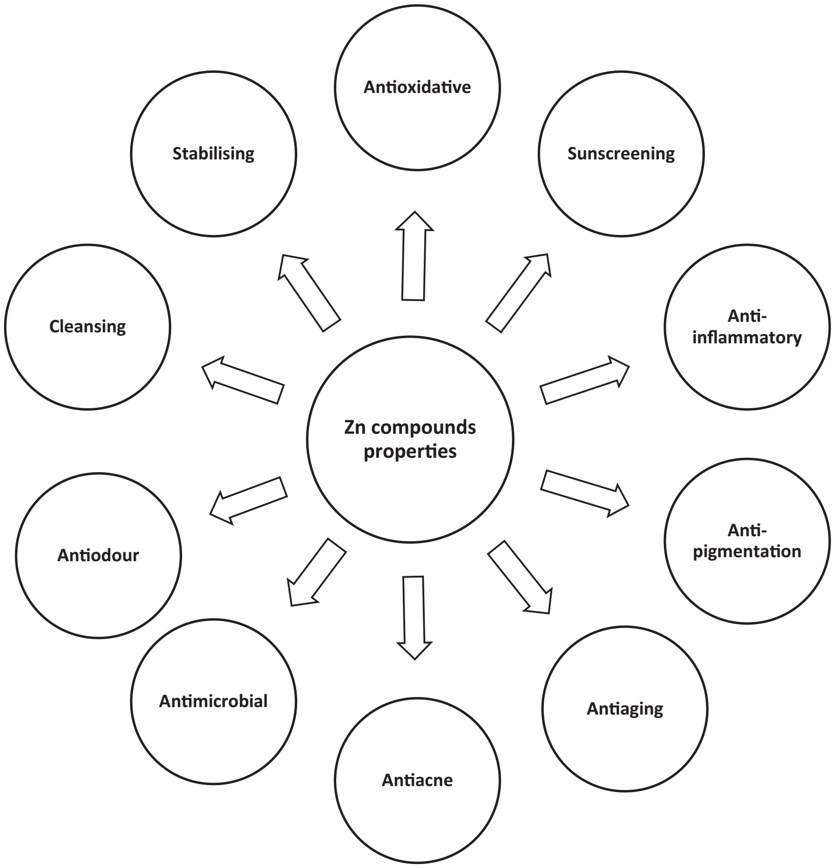

Figure 4 Functionality profile of Zn compounds.

of cancer, cardiovascular diseases and has UV-protecting properties [11,12]. However, when used in cosmetic products, Zn offers relatively few benefits to the human organism as a whole, due to its limited absorption through skin. Although most of the beneficial features of Zn are reflected in skin care products, each type of molecule possesses its own functionality profile, which is still being discovered over time (Fig. 4).

Antioxidant activity

Zinc possesses well-known antioxidant properties. The data refer not only to skin, but also to various systemic diseases. Zn compounds are therefore often employed to fight free radicals, which are responsible for causing many undesirable oxidative alterations in biomolecules, cells, tissues and organs.

In general, zinc exerts its antioxidative properties through two routes, either directly or indirectly. In the first case, Zn^{2+} ions are bound to the active centre of antioxidative enzymes. This the case of e.g. superoxide dismutase, which can incorporate zinc and copper in its structure (SOD type 1) [13]. Another example of antioxidant-boosting effect of zinc ions is a stimulating production of the protein, which is rich in sulfhydryl groups – metallothionein (MT). Its antioxidant properties derive from the high chemical affinity of its zinc-thiolate moieties to reduce other molecules; in addition to their antioxidant properties, the high-cysteine proteins also detoxify the body by binding free heavy metal ions. It has been found that zinc protects skin from immunosuppression caused by UV radiation by inducing MT production [11]. There are data, which confirm that Zn increases the activity of well-known antioxidant enzymes such as glutathione catalase (GSH) or superoxide dismutase (SOD) and reduce the induced oxidative potential by decreasing the activity of inducible nitric acid synthase (iNOS) and NADPH oxidase [14,15].

In addition, zinc also offers high complexing affinity or competitive inhibition properties to metals in different enzymes. Zn^{2+} ions may replace redox-prone copper (Cu) and iron (Fe) ions, which take part in a number of redox reactions, including those in which natural-occurring free radicals like superoxide radical anion or hydroxyl radical are created [11,14].

Divalent Zn^{2+} ions have been found to provide skin photoprotection via their indirect antioxidant properties. Zinc has demonstrated a protective effect on skin fibroblasts exposed to UVA and UVB radiation, resulting in decreased cytotoxicity and lipid peroxidation [11]. It has been proven that zinc acts as a superior lipid oxidation protector by decreasing the amount of characteristic lipid oxidation products, such as malondialdehyde, coupled dienes and hydroxyalkenoles. Zinc also has been found to protect DNA by reducing the concentration of 8′-hydroxy-2′deoxyguanosine, a well-known oxidation product of DNA [13]; also, zinc chloride significantly decreased the numbers of UV-induced DNA helix alterations in human fibroblast cultures and UVA-induced free radical level in mouse skin cell culture [16]. A similar effect has also been observed when zinc chloride was applied directly to the skin [17]. Interestingly, the antioxidant efficacy of zinc compounds is related to their bioavailability: organic chemicals with a complex structure like zinc cysteine [$Zn(Cys)_2$] demonstrated much greater antioxidant activity than simpler chemicals, such as zinc oxide, citrate, sulphate or gluconate. Its total antioxidative effect was even comparable with those of vitamin C or E [18]. Similarly, the Zn(II)-glycine complex [$Zn(Gly)_2$] (Fig. 1) not only protects against extrinsic oxidative stress, but also enhances UVB protection by inducing MT production [19]. Zn–glycine chelate was found to be better absorbed by rats *in vivo* than inorganic compounds such as zinc sulphate, oxide or carbonate and is excreted from the body more slowly [6]. Zn-Gly supplementation has also been found to improve overall oxidative stress protection and increase storage of zinc in tissues [20–22] and in a dose-dependent manner in serum and the liver [23].

Sunscreening properties

Sunscreen properties are well-known for zinc oxide. ZnO is a white powder, which is often used as a UV filter and a colourant in cosmetic products. Zinc oxide is an example of physical sunscreen of broad spectrum, which has been used for many years in cosmetic and pharmaceutical products. It most effectively blocks UV rays within the 340–400 nm band. An entire UVA range is divided into two parts with different wavelengths: 320–340 nm for UVA-2 and 340–400 nm for UVA-1, which shows that zinc oxide ensures protection against almost entire range of UVA. Zinc oxide can be used alone as a sunscreen, but is more commonly used in combination with other sunscreen agents, particularly titanium dioxide, which protects mainly against UVB (290–320 nm) [15,24]. In response to their high tendency to sediment over time, micronized forms of these physical sunscreens had become to be more popular. It is worth remembering that decreasing particle size increases UVB blocking potential and reduces UVA protection at the same time. Hence, a blend of zinc oxide and titanium oxide, which is not micronized, will offer lower level of protection across the full range of UV wavelengths that the partly micronized blend would. Therefore, to ensure an optimal UVA and UVB protection, it is recommended to use the blend of nanosized TiO_2 with mixed nanosized and large micronized ZnO particles [24]. Although ZnO was recognized to be safe when used as a sunscreen agent with the maximal concentration of 25% [25], recently it has been banned as a colourant agent for cosmetic products, because of the risk of its particles inhalation, which may lead to lungs inflammation [26].

Topical use of 1% $ZnCl_2$ has also been found to offer protection against UVA- and UVB-induced sunburn cell formation in mouse skin [11]. An important alternative for sunscreen agents is Zn–glycine complex, which has ability to induce MT, which also improves the resistance against UV-induced oxidative stress preventing from skin hyperpigmentation [19]. In spite of potential use of zinc chloride or Zn–glycine complex, zinc oxide remains nowadays the most widespread sunscreen blocking agent in cosmetic products.

Anti-inflammatory activity

Anti-inflammatory features could be considered as a derivative functionality of zinc-containing moieties, which are exactly responsible for antioxidant properties.

Zn^{2+} ions diminish reactive oxygen species (ROS) production by inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The list of ROS, which production Zn^{2+} affects, includes oxygen-based molecules comprising superoxide radical anion ($^{\cdot}O_2^{-}$), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($^{\cdot}OH$), which are produced in an aerobic environment as byproducts of normal cell metabolism. However, at high concentrations, they can cause alterations in various molecules and damage cell structures; NADPH oxidase inhibitors such as zinc might thus have a protective influence taking into account the decrease in ROS formation [14,27].

However, zinc also contributes indirectly to the dismutation of $^{\cdot}O_2^{-}$ by acting as an essential co-factor for SOD. This results in the production of H_2O_2, which is subsequently reduced to free water molecules and oxygen by catalase [14,27].

Zinc also inhibits the formation of inflammatory mediators such as nitric oxide due to inhibiting the activity of iNOS [15].

All these mechanisms have been demonstrated in animal and human models. Zinc supplementation was found to reduce the level of inflammation-causing cytokines and oxidative stress biomarkers, such as C-reactive protein [14].

Hence, Zn compounds are used in the treatment of a range of skin ailments associated with the inflammation process: acne, rosacea, seborrhoeic dermatitis, eczema, erosive pustular dermatosis and wounds of various aetiologies. Moreover, zinc-containing chemicals could be employed in the treatment of hair disorders (alopecia) and mucosal conditions (Oral Lichen Planus) [2,11,15].

The topical application of zinc oxide paste and zinc sulphate has been found to be effective in treating diaper dermatitis and hand eczemas. Zinc oxide and zinc carbonate have also demonstrated soothing properties and hence have been used to treat pruritus [15].

The anti-inflammatory effect of zinc peroxide nanoparticles (ZnO_2-NPs) was compared with that of standard aspirin, which is the well-known example of anti-inflammatory drug. The nanoparticles showed significant anti-inflammatory activity towards *Pseudomonas aeruginosa* PA6 and *Aspergillus niger* AN4 strains, with regard to membrane stabilization, proteinase inhibition and albumin denaturation [28].

Anti-pigmentation properties

Of all known Zn compounds, Zn–glycine complex [$Zn(Gly)_2$] (Fig. 1) is believed to have the greatest anti-pigmentation potential, which has been attributed to its antioxidant and sunscreening properties [19]. It is a well-known MT-inducer, and moreover, it activates γ-glutamyl cysteinyl synthetase (γ-GCS). [$Zn(Gly)_2$] exhibits an ability to decrease oxidative stress by preventing intracellular ROS formation [8]. It is also possible that Zn is a co-factor which plays a role in tyrosine metabolism, oxidation and conversion to melanin [1].

Zinc oxide is also used in sunscreening products used for melasma treatment.

Moreover, the topical application of 10% zinc sulphate solution twice a day for three months was found to improve a skin condition with melasma, but not significantly, and hence could not be considered a regular mode of melasma treatment [15]. It is important to note that the maximum zinc concentration allowed in cosmetic products in the European Union is 1% [29].

Anti-ageing properties

The anti-ageing properties of Zn-containing compounds are not well-established. Zn–glycine complex is believed to act as anti-ageing agent by preventing ROS formation [8]. Moreover, cream with 0.1% copper-zinc malonate was found to have a positive effect on photoaged facial skin over an eight-week course of treatment, with beneficial results being observed in group of 21 female patients: significant regeneration of skin elastic fibres was observed, leading to wrinkle smoothing [15, 30].

Anti-acne activity

Acne vulgaris is a disease that is incidental with the presence and activity of bacteria, inflammation and excess sebum production and keratinization. It is a common disease which affects almost 90–95% of teenagers [15].

Zn compounds have well-established anti-acne properties. Although Zn-containing products are not first choice antimicrobial drugs, they are often used in cases of antibiotic-resistant *Propionibacterium acne* bacteria. Zn compounds have been used to treat acne due to its ability to reduce the inflammation of acne lesions and inhibit sebum production and are administrated not only topically, but also orally.

The oral form of Zn, typically zinc sulphate or the better absorbed zinc gluconate, is recommended for the treatment of moderate and severe acne, and its effectiveness is comparable to that of systemic tetracyclines, such as minocycline or oxytetracycline. However, as oral administration of Zn salts is associated with side effects, such as nausea, diarrhoea or vomiting, Zn salts are used as supporting agents rather than as the main remedy.

Otherwise, in case of topical administration, Zn compounds are widely used in cosmetic formulas due to their anti-inflammatory properties and an ability to decrease number of *P. acnes* bacteria, by blocking of the *P. acnes* lipases and reducing of free fatty acids' level. Zinc sulphate is used rarely, because of its high irritating potential [15].

For acne treatment, the astringent properties of Zn salts are also beneficial. One excellent example is zinc oxide, which has also been found to have sebum regulating properties, and another is zinc 2-pirrolidone 5-carboxylate (Zn PCA) (Fig. 5). It offers significant benefits for acne-prone skin because, as well as its astringent properties, it exhibits antimicrobial properties against *P. acnes* and *S. epidermidis* [1].

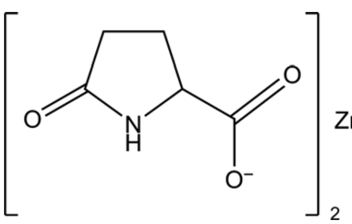

Figure 5 Structure of zinc 2-pirrolidone 5-carboxylate.

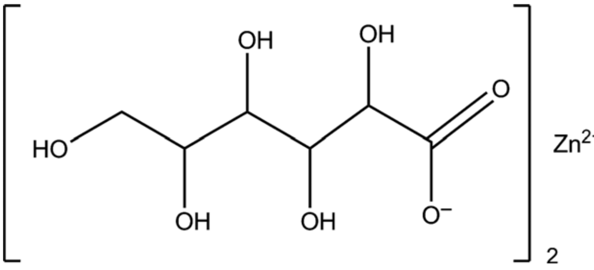

Figure 6 The structure of zinc gluconate.

Zinc gluconate (Fig. 6) is known to be effective in healing inflammatory acne and possesses antimicrobial activity against *P. acnes*. It is also effective against erythromycin-resistant *P. acne* strains. An *in vivo* study carried out on a group of thirty patients with inflammatory acne found that treatment with 30 mg of zinc gluconate per day for two months was effective and caused a reduction in the number of inflammatory lesions, regardless of the presence of erythromycin-resistant *P. acne* strains. The addition of zinc gluconate to the culture medium of *P. acnes* was also found to reduce the resistance of *P. acne* strains to erythromycin [31]. Another publication indicates that Zn appears to increase the total topical absorption of erythromycin, which could constitute a probable explanation of decreasing resistance to this antibiotic [15].

Another research on *Propionibactrium acnes* has showed that ZnO of three different particle sizes mixed with citric acid (CA) may be a good candidate for the prevention of and treatment of acne. The smallest particles (<50 nm) showed the best antimicrobial activity. What interesting, the mixture of the two ingredients ZnO : CA (1 : 1) resulted the higher antimicrobial activity than ZnO and CA separately did [32].

The efficacy of oral intake of capsule formulations containing lactoferrin, zinc and vitamin E has been confirmed for mild-to-moderate acne vulgaris [33].

Antibacterial activity

It should be emphasized that it is difficult to compare antimicrobial agents because their activity is often estimated under varying conditions, that is incubation time, type of culture medium, type of microbial strain and choice of unit (e.g. μM, mg L^{-1} and other).

The optimal level of Zn^{2+} ions in microbial cells has been found to range from 10^{-7} to 10^{-5} M depending on the strain. It has been observed that concentrations above 10^{-4} M disturb the homoeostasis of Zn^{2+} ions and enhance its permeability through the cell membrane, and this has cytotoxic effects on prokaryotes. Although antimicrobial activity is mainly influenced by Zn^{2+} concentration, the form of the Zn compound itself also has an effect [7].

Zinc acetate has greater antibacterial potential against *Staphylococcus aureus* and *Staphylococcus epidermidis* than *Pseudomonas aeruginosa* [34], with the effectiveness above 11 mmol L^{-1} calculated on Zn^{2+} ions. In turn, long-term contact with 100 μg g^{-1} of Zn decreased the generation of *Aspergillus brasiliensis* spores [7,34]. Zinc chloride also exhibits dose-related growth-inhibiting potential against *Escherichia coli* [7]. Zinc sulphate ($ZnSO_4 \cdot 7H_2O$) is used in oral care products, typically at concentrations of 0.02–0.5% calculated on Zn^{2+} content. In addition, it has been established that using Zn salts in such products might inhibit tartar formation [1].

The dose-dependent effect has been also observed for zinc oxide and zinc gluconate. The Challenge Test, used by the pharmaceutical and cosmetic industry to check microbiological safety by calculating the Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC), found zinc gluconate salt to have higher antimicrobial activity than ZnO. Zinc gluconate tends to have greater efficacy against *A. brasiliensis*, *E. coli* and *C. albicans*, but zinc oxide supernatant is more active against *S. aureus* and *P. aeruginosa* [7].

A variety of antimicrobial mechanisms can be observed depending on the tested Zn compound; however, a key distinction can be made between those used by soluble species and by insoluble species. The former has two postulated mechanisms of action: in the first, interaction between Zn^{2+} ions and cell membrane leads to its

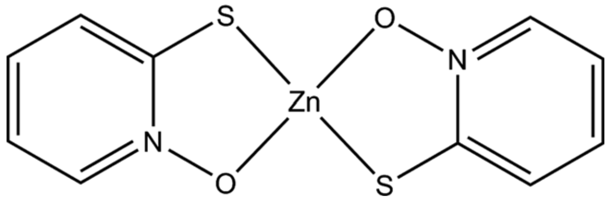

Figure 7 Outline of zinc pyrithione's structure (ZPT).

destabilization and enhanced permeability, while in the second, the nucleic acids are thought to interact with the Zn^{2+} ions, causing dysfunctions in the respiratory enzymes. However, the exact mechanism of soluble compounds' activity remains unclear, due to its complexity. Three mechanisms have been proposed for insoluble Zn compounds like ZnO: production of reactive oxygen species (ROS) [35,36], the destruction of cell walls by direct contact with microbial membranes, and the intrinsic cytotoxic effect obtained by releasing Zn^{2+} ions [7,37].

Although the antibacterial activity of regular ZnO has been relatively well investigated, the activity of ZnO nanoparticles remains poorly studied. Nevertheless, ZnO nanoparticles have demonstrated significant antibacterial activity on a broad spectrum of microorganisms, with greater activity against *S. aureus* than other metal oxide nanoparticles. It has been found that the activity of ZnO is dependent on the particle size and the presence of visible light [37]: the MIC value against *S. aureus* was found to be 1 mM (or 80 μg mL^{-1}) for smaller ZnO nanoparticles (ca. 8 nm), but 15 mM (or 1.2 mg mL^{-1}) for larger ones (50–70 nm) [32,38]. The antimicrobial activities of water suspensions of nanosized ZnO, TiO_2 and SiO_2 were compared against *Bacillus subtilis* and *Escherichia coli*. Better results were obtained for *B. subtilis.* The study also confirmed that ZnO nanoparticles were the most active among other metal oxide particles, and their activity was proportional to decreasing particle size [32,37,39].

Hence, Zn-containing chemicals may serve as an important group of preservatives in cosmetic and pharmaceutical products.

Antifungal activity

Zn compounds also demonstrate antifungal activity. An excellent example is the Zn complex with pyridinethione (Fig. 7), commonly known as pyrithione. Zinc pyrithione (ZPT) demonstrates anti-dandruff properties. It has an ability to reduce the activity of *Pityrosporum* (*Malassezia*), a pathogenic species responsible for such skin conditions as dandruff and seborrhoeic dermatitis [1,15,40]. Zinc pyrithione is often used in anti-dandruff shampoo (AD), and its low water solubility allows it to remain on the scalp after rinsing. To increase deposition of ZPT onto the scalp, a dual-active AD shampoo containing both ZPT and CBZ (climbazole) has been tested with satisfactory results [41]. Such dual-active AD shampoos not only reduce *Malassezia furfur* regrowth, but also may enhance sensory benefits by selecting suitable conditioning ingredients [42]. In addition, as it has no impact on the odour and colour of the final formulation, it can be easily incorporated into new products.

The mechanism of the antifungal action of ZPT appears quite complex. It has been demonstrated that ZPT depolarizes the cell membrane and prevents transport through it [43,44], while it has also been found that its antifungal efficacy depends on its iron-blocking properties [45]. Recently, it was established that fungal growth inhibition is related to an increase in the copper concentration and the destruction of the iron-sulphur protein clusters crucial for fungal metabolism [40].

It is worth underlining that ZPT has also high antibacterial efficacy: thermoplastic elastomers (TPE) incorporated with zinc pyrithione (ZPT) were found to demonstrate a good inhibitory effect towards *Escherichia coli* and *Staphylococcus aureus* [46]. This material coated with ZPT was also evaluated against *Aspergillus niger, Candida albicans* and *Cladosporium cladosporioides* fungi by the measurement of inhibition zones, which amounted to 7 mm, 2 mm and 6 mm, respectively [46].

The antifungal activity of biosynthesized ZnO nanoparticles (ZnONps) stabilized by *Adhatoda vasica* proteins was studied against *Candida* sp., *Fusarium* sp., *Microsporum audouinii, Trichophyton rubrum* and *Aspergillus fumigatus.* The obtained MIC (MFC) values were 256 (256), 64 (128), 256 (512), 64 (128) and 32 (32) μg mL^{-1}, respectively. The most pronounced antifungal effect was noticed against *Aspergillus fumigatus.* Most importantly, the cream with ZnONps exhibited significant inhibitory activity towards *Candida* sp., which showed resistance against a commercial antifungal cream (2%) [47].

Zinc undecylenate (ZnUA) and free undecylenic acid (UA) have been known as effective antifungal agents. They have been used in medicine as ingredients of many topical preparations [48].

Anti-odour activity

Two Zn compounds that do not show antibacterial activity, that is zinc glycinate and zinc ricinoleate have been found to have anti-odour activity. This activity is believed to be based on the inhibition of two hydrolytic enzymes produced by bacteria found in the human axilla area. There are two groups of bacteria known to colonize the axilla: *Coryneform bacteria* (known also as lipophilic diphteroids] responsible for the production of odour associated with delta-16 steroids, and micrococci such as *Staphylococcus epidermidis* which tend to produce isovaleric acid odours. Enzymes such as aryl sulfatase and beta-glucuronidase show hydrolytic activity for appropriate sulphate or glucuronide derivatives. In the case of sweat and odour, their ester decomposing effectiveness is connected with realizing free volatile steroid 5-α-androstanol from their following esters: 5,α-androst-16-ene-3,β-ol glucuronide by beta-

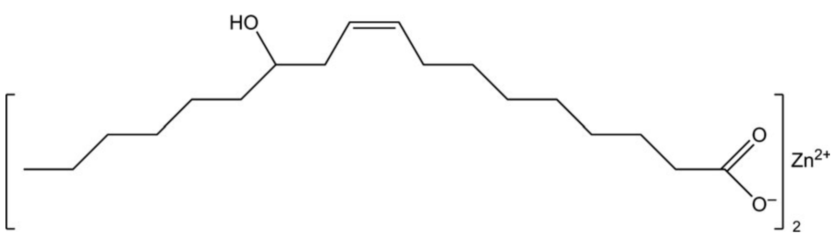

Figure 8 Structure of zinc ricinoleate.

glucuronidase and from 5,α-androst-16-ene-3,β-ol sulphate by aryl sulfatase. As free 5-α-androstanol is one of the odorants known to be present in the axilla, inhibition of these two enzymes is important for anti-odour activity [1,49].

Despite the fact that zinc ricinoleate (Fig. 8) does not possess bactericidal properties, it has a deodorizing effect which can be maintained for up to 24 h after topical application. This has been attributed to its high reactivity with low molecular weight organic compounds containing -SH and -NH groups, which are abundantly released from sweat by microorganisms. Zn ricinoleate has also an ability to react with free fatty acids. Interestingly, Zn salts with stearic and oleic acids do not exhibit similar odour-eliminating properties [1,50].

Of the new Zn-containing materials, which have been created, a hybrid (ZnAl–Ag_{NPs}) based on silver nanoparticles and ZnAl layered double hydroxides (ZnAl LDHs) and raw ZnAL LDH appears of interest. ZnAl-Ag_{NPs} was found to be ten times more effective than the reference Zn ricinoleate in a study of deodorant activity against a fatty acid mixture. In addition, ZnAl-Ag_{NPs} also shows antibacterial activity against *E. coli* [51].

Zinc oxide also has deodorizing properties, because of converting short and medium-chain free fatty acids into water-insoluble, nonvolatile salts. ZnO is an essential ingredient of baby products for use in the diaper area, thanks to its astringent and absorbing features and good skin covering potential [1].

A 15% solution of Zn sulphate was found to have high efficiency in reducing foot odour in 70% of patients in a 2-week study. This high level of clearance was sustained by applying the solution as maintenance therapy once a week [52]. Although this solution was found to have high efficiency, the Zn concentration in cosmetic products is limited to 1% in the European Union [29], and so further studies have to be performed to confirm the effectiveness at lower concentrations.

Zn propionate, caprylate and undecylenate are also often found in foot care products, as they offer antiseptic and deodorizing properties and the ability to inhibit bacterial growth [1,48].

Cleansing properties

One example of a Zn compound used in skin cleansing products is Zinc Lauryl Ether Sulphate (ZnLES). It combines the antibacterial, deodorizing and sebum-reducing potential of Zn^{2+} ions with the detergency and good foaming potential characteristic of alkyl ether sulphate derivatives. One advantage of this Zn salt over other Lauryl Ether Sulphate salts is its lower potential for skin irritation. Its critical micelle concentration value (CMC) is lower than that of the widely used Sodium Lauryl Ether Sulphate (SLES) and comparable to that of Magnesium Lauryl Ether Sulphate (MgLES). The maximal recommended concentration of ZnLES in skin cleansing products is 12.5%. From a technological point of view, it is necessary to adjust the pH around 4.5–6.0 before adding this substance to final product. It is crucial to avoid zinc hydroxide precipitation, as this results in the product losing its transparency [1].

Stabilizing property

Zinc salt with stearic acid possesses stabilizing property and thus is utilized in many personal care products. That is why zinc stearate is a common additive for w/o emulsions, because it has the ability to inhibit phase separation by controlling viscosity. In addition, zinc stearate and zinc myristate are also used as adhesion enhancers in face powders [1].

Conclusion

Zn compounds are widely used in cosmetic formulations and are often included as active or supportive ingredients in a wide range of formulations. The continuing popularity of cosmetics, which are based on Zn compounds, attests to their excellent biological properties and good skin tolerance. Two of the most important properties offered by Zn compounds are their antimicrobial and antioxidative effects, which allow treatment of skin ailments, including acne, dandruff, dermatitis, psoriasis, eczema or diaper rash. The anti-acne, anti-odour and anti-dandruff properties are derived from its antimicrobial activity, whereas the anti-inflammatory, anti-pigmentation, sunscreening properties from its antioxidative potential. In turn, these latter properties combine to anti-ageing activity.

The most widely used Zn compound in personal care formulations is zinc oxide. It possesses a variety of beneficial UV-protective, anti-acne, antibacterial, astringent, anti-odour and anti-inflammatory properties for skin, among others. In coloured cosmetics, it is used for whitening cosmetic products as an addition to powders and fluids. ZnO is non-toxic, non-sensitizing and biosafe ingredient. However, it occurs to be hazardous to inhale ZnO nanoparticles fumes [26]. The most promising Zn compound seems to be Zn–glycine complex as it displays a wide spectrum of biological activity, but is not toxic and does not cause skin irritation. The stabilizing and cleansing properties of the mentioned Zn salts are generally associated with the properties of the anions, but Zn^{2+} ions were most probably selected as cations in these salts because of their positive impact on skin, that is their lack of toxicity and irritation.

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References

1. Frydrych, A., Arcf, J. and Kasiura, K. Zinc: a critical importance element in cosmetology. *J. Appl. Cosmetol.* **22**, 1–13 (2004).
2. Nitzan, Y.B. and Cohen, A.D. Zinc in skin pathology and care. *J. Dermatol. Treat.* **17**, 205–210 (2006).
3. Krishnamurthy, V.M., Kaufman, G.K., Urbach, A.R., Gitlin, I., Gudiksen, K.L., Weibel, D.B. and Whitesides, G.M. Carbonic anhydrase as a model for biophysical and physical-organic studies of proteins and protein–ligand binding. *Chem. Rev.* **108**, 946–1051 (2008).
4. EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on Dietary Reference Values for zinc. *EFSA Journal* **12**, 3844 (2014).
5. Barceloux, D.G. Zinc. *J. Toxicol. Clin. Toxicol.* **37**, 279–292 (1999).
6. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from

the Commission on certain bisglycinates and glycinate nicotinate as sources for copper, zinc, calcium, magnesium and chromium. *The EFSA Journal.* **718**, 1–266 (2008).

7. Pasquet, J., Chevalier, Y., Pelletier, J., Couval, E., Bouvier, D. and Bolzinger, M.-A. The contribution of zinc ions to the antimicrobial activity of zinc oxide. *Colloids Surfaces A: Physicochem. Eng. Aspects.* **457**, 263–274 (2014).
8. Masaki, H. Possible use of zinc ions for antipigmentation and anti-wrinkling skin care. *Yakugaku Zasshi* **132**, 261–269 (2012).
9. Fortes, A.D., Howard, C.M., Wood, I.G. and Gutmann, M.J. Glycine zinc sulfate pentahydrate: redetermination at 10 K from time-of-flight neutron Laue diffraction. *Acta Cryst.* **E72**, 1438–1445 (2016).
10. Tepavitcharov, S., Havlíĉek, D., Matulková, I. *et al.* New zinc-glycine-iodide complexes as a product of equilibrium and non-equilibrium crystallization in the Gly–ZnI_2–H_2O system. *J. Mol. Struct.* **1120**, 42–49 (2016).
11. Rostan, E.F., DeBuys, H.V., Madey, D.L. and Pinnell, S.R. Evidence supporting zinc as an important antioxidant for skin. *Int. J. Dermatol.* **41**, 606–611 (2002).
12. Lansdown, A.B., Mirastschijski, U., Stubbs, N., Scanlon, E. and Agren, M.S. Zinc in wound healing: Theoretical, experimental, and clinical aspects. *Wound Repair Regen.* **15**, 2–16 (2007).
13. Frydrych, A., Arct, J. and Kasiura, K. Antioxidative role of metals in the skin. *J. Appl. Cosmetol.* **26**, 143–157 (2008).
14. Prasad, A.S. Zinc is an antioxidant and anti-inflammatory agent: its role in human health. *Front. Nutrit.* **1**, 1–10 (2014).
15. Gupta, M., Mahajan, V.K., Mehta, K.S. and Chauhan, P.S. Zinc therapy in dermatology: a review. *Dermatol. Res. Pract.* **2014**, 11 (2014) Article ID 709152.
16. Sakurai, H., Yasui, H., Yamada, Y., Nishimura, H. and Shiqemoto, M. Detection of reactive oxygen species in the skin of live mice and rats exposed to UVA light: a research review on chemiluminescence and trials for UVA protection. *Photochem. Photobiol. Sci.* **4**, 715–720 (2005).
17. Sakurai, H., Yasui, Y. and Mishina, K. Protective effect of zinc ion on ultraviolet lightinduced skin damage: studies on imaging of ROS by chemiluminescence method. *Biomed. Res. Trace Elem.* **14**, 17–21 (2003).
18. Chien, X.X., Zafra-Stone, S., Bagchi, M. and Bagchi, D. Bioavailability, antioxidant and immune-enhancing properties of zinc methionine. *BioFactors* **27**, 231–244 (2006).
19. Masaki, H., Ochiai, Y., Okano, Y. *et al.* A zinc(II)-glycine complex is an effective inducer of metallothionein and removes oxidative stress. *J. Dermatol. Sci.* **45**, 73–75 (2007).
20. Ma, W., Niu, H., Feng, J. and Wang, Y. Effects of zinc glycine chelate on oxidative stress, contents of trace elements, and intestinal morphology in broilers. *Biol. Trace Elem. Res.* **142**, 546–556 (2011).
21. Yue, M., Fang, S.L., Zhuo, Z., Li, D.D. and Feng, J. Zinc glycine chelate absorption characteristics in Sprague Dawley rat. *J. Anim. Physiol. Anim. Nutr.* **99**, 457–464 (2015).
22. Kwiecień, M., Winiarska-Mieczan, A., Milczarek, A. and Klebaniuk, R. Biological response of broiler chickens to decreasing dietary inclusion levels of zinc glycine chelate. *Biol. Trace Elem. Res.* **175**, 204–213 (2017).
23. Huang, D., Hu, Q., Fang, S. and Feng, J. Dosage effect of zinc glycine chelate on zinc metabolism and gene expression of zinc transporter in intestinal segments on rat. *Biol. Trace Elem. Res.* **171**, 363–370 (2016).
24. Smijs, T.G. and Pavel, S. Titanium dioxide and zinc oxide nanoparticles in sunscreens: focus on their safety and effectiveness. *Nanotech. Sci. Appl.* **4**, 95–112 (2011).
25. Kim, K.B., Kim, Y.W., Lim, S.K. *et al.* Risk assessment of zinc oxide, a cosmetic ingredient used as a UV filter of sunscreens. *J. Toxicol. Environ. Health. B. Crit. Rev.* **20**, 155–182 (2017).
26. http://eurlex.europa.eu/legalcontent/EN/TXT/PDF/?uri=CELEX:32017R1413&from=EN
27. Dayem, A.A., Hossain, M.K., Lee, S.B. *et al.* The role of reactive oxygen species (ROS) in the biological activities of metallic nanoparticles. *Int. J. Mol. Sci.* **18**, 120 (2017).
28. Ali, S.S., Morsy, R., El-Zawawy, N.A., Fareed, M.F and Bedaiwy, M. Synthesized zinc peroxide nanoparticles (ZnO_2-NPs): a novel antimicrobial, anti-elastase, anti-keratinase, and anti-inflammatory approach toward polymicrobial burn wounds. *Int. J. Nanomed.* **12**, 6059–6073 (2017).
29. Safety Assessment of Zinc Salts as Used in Cosmetics. Cosmetic Ingredient Review. (2017). October 12.
30. Mahoney, M.G., Brennan, D., Starcher, B., Faryniarz, J., Ramirez, J., Parr, L. and Uitto, J. Extracellular matrix in cutaneous ageing: the effects of 0.1% copper–zinc malonate-containing cream on elastin biosynthesis. *Exp. Dermatol.* **18**, 205–211 (2009).
31. Dreno, B., Foulc, P., Reynaud, A., Moyse, D., Habert, H. and Richet, H. Effect of zinc gluconate on propionibacterium acnes resistance to erythromycin in patients with inflammatory acne: in vitro and in vivo study. *Eur. J. Dermatol.* **15**, 152–155 (2005).
32. Bae, J.Y. and Park, S.N. Evaluation of antimicrobial activities of ZnO, citric acid and a mixture of both against *Propionibacterium acnes*. *Int. J. Cosmet. Sci.* **38**, 550–557 (2016).
33. Chan, H., Chan, G., Santos, J., Dee, K. and Co, J.K. A randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of lactoferrin with vitamin E and zinc as an oral therapy for mild to moderate acne vulgaris. *Int. J. Dermatol.* **56**, 686–690 (2017).
34. Atmaca, S., Gul, K. and Clcek, R. The effect of zinc on microbial growth. *Tr. J. Med. Sci.* **28**, 595–597 (1998).
35. Zhang, L., Jiang, Y., Ding, Y., Povey, M. and York, D. Investigation into the antibacterial behaviour of suspensions of ZnO nanoparticles (ZnO nanofluids). *J. Nanopart. Res.* **9**, 479–489 (2007).
36. Xia, T., Kovochich, M., Liong, M. *et al.* Comparison of the mechanism of toxicity of zinc oxide and cerium oxide nanoparticles based on dissolution and oxidative stress properties. *ACS Nano* **2**, 2121–2134 (2008).
37. Raghupathi, K.R., Koodali, R.T. and Manna, A.C. Size-dependent bacterial growth inhibition and mechanism of antibacterial activity of zinc oxide nanoparticle. *Langmuir* **27**, 4020–4028 (2011).
38. Jones, N., Ray, B., Ranjit, K.T. and Manna, A.C. Antibacterial activity of ZnO nanoparticle suspensions on a broad spectrum of microorganisms. *FEMS Microbiol. Lett.* **279**, 71–76 (2008).
39. Adams, L.K., Lyon, D.Y. and Alvarez, P.J. Comparative eco-toxicity of nanoscale TiO_2, SiO_2 and ZnO water suspensions. *Water Res.* **40**, 3527–3532 (2006).
40. Reeder, N.L., Xu, J., Youngquist, R.S., Rust, R.C. and Saunders, C.W. The antifungal mechanism of action of zinc pyrithione. *Br. J. Dermatol.* **165**(Suppl 2), 9–12 (2011).
41. Chen, G., Miao, M., Hoptroff, M., Fei, X., Collins, L.Z., Jones, A. and Jansee, H.-G. Sensitive and simultaneous quantification of zinc pyrithione and climbazole deposition from anti-dandruff shampoos onto human scalp. *J. Chromatogr. B* **1003**, 22–26 (2015).
42. Turner, G.A., Matheson, J.R., Li, G.-Z., Fei, X.-Q., Zhu, D. and Baines, F.L. Enhanced efficacy and sensory properties of an anti-dandruff shampoo containing zinc pyrithioneand climbazole. *Int. J. Cosmet. Sci.* **35**, 78–83 (2013).
43. Ermolayeva, E. and Sanders, D. Mechanism of pyrithione-induced membrane depolarization in Neurospora crassa. *Appl. Environ. Microbiol.* **61**, 3385–3390 (1995).

44. Chandler, C.J. and Segel, I.H. Mechanism of the antimicrobial action of pyrithione: effects on membrane transport, ATP levels, and protein synthesis. *Antimicrob. Agents Chemother.* **14**, 60–68 (1978).
45. Yasokawa, D., Murata, S., Iwahashi, Y., Kitaqawa, E., Kishi, K., Okumura, Y. and Iwahashi, H. DNA microarray analysis suggests that zinc pyrithione causes iron starvation to the yeast Saccharomyces cerevisiae. *J. Biosci. Bioeng.* **109**, 479–486 (2010).
46. Pittol, M., Tomachesk, I.D., Simões, D.N., Ribeiro, V.F. and Santana, R.M.C. Antimicrobial performance of thermoplastic elastomers containing zinc pyrithione and silver nanoparticles. *Mater. Res.* **20**, 1266–1273 (2017).
47. Sonia, S., Linda, J.K.H., Ruckmani, K. and Sivakumar, M. Antimicrobial and antioxidant potentials of biosynthesized colloidal zinc oxide nanoparticles for a fortified cold cream formulation: A potent nanocosmeceutical application. *Mater. Sci. Eng., C* **79**, 581–589 (2017).
48. Nikolov, A. and Ganchev, D. Effect of zinc undecylenates on plant pathogenic fungi. *Bulg. J. Agricul. Sci.* **16**, 220–226 (2010).
49. Froebe, C., Simone, A., Charig, A. and Eigen, E. Axillary malodor production: A new mechanism. *J. Soc. Cosmet. Chem.* **41**, 173–185 (1990).
50. Kuhn, H., Müller, F., Peggau, J. and Zekorn, R. Mechanism of the odor-adsorption effect of zinc ricinoleate. A molecular dynamics computer simulation. *J. Surfact. Deterg.* **3**, 335–343 (2000).
51. Ballarin, B., Mignani, A., Mogavero, F., Gabbanini, S. and Morigi, M. Hybrid material based on ZnAl hydrotalcite and silver nanoparticles for deodorant formulation. *Appl. Clay Sci.* **114**, 303–308 (2015).
52. Sharquie, K.E., Noaimi, A.A. and Hameed, S.D. Topical 15% zinc sulfate solution is an effective therapy for feet odor. *J. Cosmet., Dermatol. Sci. Appl.* **3**, 203–208 (2013).