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The contribution of zinc ions to the antimicrobial activity of zinc oxide

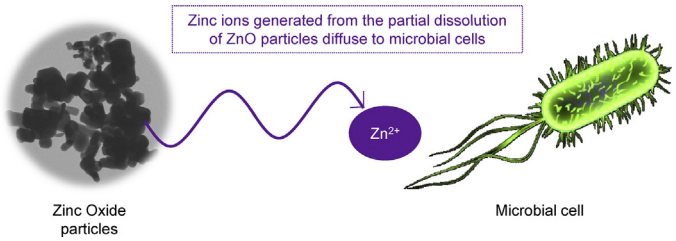
Julia Pasquet[a,b], Yves Chevalier[b,*], Jocelyne Pelletier[b], Emmanuelle Couval[a], Dominique Bouvier[a], Marie-Alexandrine Bolzinger[b]

[a] Strand Cosmetics Europe, 124 route du Charpenay, 69210 Lentilly, France
[b] Université Claude Bernard Lyon 1, Laboratoire d'Automatique et de Génie des Procédés (LAGEP), CNRS UMR 5007, 43 bd 11 Novembre, 69622 Villeurbanne, France

HIGHLIGHTS

- Proteins contained in a broth medium increase the solubility of ZnO particles.
- The respective activities of ZnO and Zn^{2+} show specificity with respect to the microorganisms.
- The contribution of Zn^{2+} to the antimicrobial activity of ZnO depends on the strain.
- The dissolution process depends on time, ZnO concentration, and type of ZnO powder.
- The combination of the three antimicrobial mechanisms of ZnO is beneficial.

GRAPHICAL ABSTRACT



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ABSTRACT

Zinc ions (Zn^{2+}) exhibit antimicrobial activity against various bacterial and fungal strains. The partial dissolution of zinc oxide (ZnO) particles releases Zn^{2+} ions in aqueous suspension that contributes to the antimicrobial activity of ZnO. In addition to the activity of the soluble zinc species that is common with water-soluble zinc salts, ZnO combines two additional mechanisms of antimicrobial activity that supplement its activity as preservative in topical formulations: generation of reactive oxygen species and by direct contact to the cells walls. The present study aims at the evaluation of the contribution of the soluble zinc species to the antimicrobial activity of ZnO on microbial cultures in broth medium and the investigation of the dissolution of zinc from ZnO suspensions. The antimicrobial activities against the five microorganisms of the Challenge Tests were measured for suspensions of three ZnO grades in broth, and for the isolated liquid phase of the suspensions containing soluble zinc species. The Zn^{2+} released in the broth brought about a significant contribution to the overall antimicrobial activity of ZnO. The complexation of Zn^{2+} ions by the components of the broth increased the solubility of the zinc in the liquid medium. The respective activities of the soluble zinc species and ZnO particles showed specificity with respect to the microbial strains. Dissolution was faster for high concentrations of ZnO and for ZnO powders of larger specific area. Such conditions led to a better antimicrobial efficacy of ZnO powders. ZnO appears an advantageous alternative to soluble zinc salts such as zinc gluconate.

* Corresponding author. Tel.: +33 4 72 43 18 77; fax: +33 4 72 43 16 82.
E-mail addresses: jpasquet@strandcosmeticseurope.com (J. Pasquet), chevalier@lagep.univ-lyon1.fr (Y. Chevalier), jocelyne.pelletier@univ-lyon1.fr (J. Pelletier), ecouval@strandcosmeticseurope.com (E. Couval), dbouvier@strandcosmeticseurope.com (D. Bouvier), bolzinger@lagep.univ-lyon1.fr (M.-A. Bolzinger).

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1. Introduction

Zinc oxide (ZnO) is an efficient antimicrobial agent that acts by means of several mechanisms involving different chemical species. Three distinct mechanisms of action have been put forwards in the literature: (i) the production of reactive oxygen species (ROS) because of the semiconductive properties of ZnO [1,2,3], (ii) the destabilization of microbial membranes upon direct contact of ZnO particles to the cell walls [4–6], and (iii) the intrinsic antimicrobial properties of Zn^{2+} ions released by ZnO in aqueous medium [7–9]. The present study aims at investigating the contribution of the soluble species released by ZnO, especially Zn^{2+}.

Zinc is an essential element for microorganisms and higher organisms because it is involved in many vital cellular reactions at its low endogenous concentrations [10–13]. The concentration of zinc is 10^{-4} M in blood [14]. Optimal rates of this cofactor are needed for catalytic and structural activities [14,15]. Zinc concentration is regulated under physiological conditions by several transporters [15–17], so that Zn^{2+} ions are essentially nontoxic to higher organisms [3]. Homeostasis regulates zinc uptake by cells, but it does not control zinc adsorption to cell membranes however. Increase of Zn^{2+} concentrationsabove optimal levels (typically between 10^{-7} M and 10^{-5} M depending on the microbial strain [18]) perturbs Zn^{2+} homeostasis and allows entry of Zn^{2+} inside cells, so that zinc starts being cytotoxic to prokaryotes above a concentration of $\sim 10^{-4}$ M [18,19]. Therefore, Zn^{2+} displays an antimicrobial activity and could act as either antibacterial or antifungal agent. The antimicrobial properties of Zn^{2+} have been known since a long time, both against bacterial [20–22] and fungal strains [23].

According to several reports on water-soluble zinc salts, the antimicrobial activity of Zn^{2+} depends on its concentration and contact duration. Zinc chloride acts in a dose-dependent manner against *Escherichia coli* [21,22]. Zinc acetate exhibits an antibacterial activity on *Pseudomonas aeruginosa* and *Staphylococcus aureus* for zinc concentrations above 11 mmol L^{-1} [20]. Moreover, a prolonged contact of zinc (at 100 $\mu g\, g^{-1}$) to *Aspergillus brasiliensis* spores inhibits their germination by 25% [23]. These antimicrobial activities were explained by two mechanisms, both leading to cell death: (i) a direct interaction with microbial membranes leading to membrane destabilization and enhanced permeability [24]; (ii) an interaction with nucleic acids and deactivation of enzymes of the respiratory system [25].

In dermatological products, zinc ions are interesting biocides and/or antimicrobial preservatives provided that high enough concentrations of Zn^{2+} are generated. The previously mentioned zinc salts can be simply dissolved in the aqueous medium. An alternative is solid powder such as ZnO particles that release Zn^{2+} in the aqueous medium. It is indeed recognized that part of the antimicrobial activity of ZnO particles originates from their ability to partially dissolve in aqueous media [26,27]. Release of Zn^{2+} would contribute to the global antimicrobial properties of this inorganic powder [7,29]. Nevertheless, the contribution of Zn^{2+} to the antimicrobial activity of ZnO is still unclear. Since ZnO particles exhibit two additional antimicrobial mechanisms with respect to zinc salts (ROS and direct contact) the combination of these three types of action broadens the antimicrobial spectrum of ZnO compared to zinc salts.

The present study has been focused on the contribution of zinc cations generated from the partial dissolution of ZnO particles in aqueous media to the global antimicrobial action. Even though the antimicrobial mechanism of Zn^{2+} has been disclosed, the antimicrobial activity of ZnO *via* a contribution of Zn^{2+} is still under debate because of the complexity of the underlying phenomena. According to Sawai [28] and Jiang et al. [6], the contribution of Zn^{2+} to the antimicrobial efficacy of ZnO particles would be minor because too low concentrations of soluble zinc species are released from the dissolution of ZnO particles. In other instances reported in the field of dentistry applications, the contribution of Zn^{2+} is predominant [30,31]. The aim of the present work was the assessment of the contribution of soluble ionic species of zinc to the antimicrobial efficacy of ZnO powders, as well as the factors that influence the dissolution of the particles. Indeed, it has been reported that the dissolution phenomenon was influenced by numerous parameters sorted into two types:

- the chemistry of the environmental media such as the pH [32,33], the duration of exposure [34–36], UV irradiation [32,37], the presence of other substances [33,38] or microorganisms [39–41];
- the physicochemical properties of the particles such as the elementary particle size [35,42,43], their porosity [44], their shape [35], their concentration [45].

The impact of all these parameters is not fully understood.

In order to use ZnO particles as an efficient antimicrobial preservative in cosmetic and dermopharmaceutical products, it was firstly aimed at discriminating the contribution of zinc cations generated by ZnO particles from the overall antimicrobial activity, and secondly identifying the parameters which directly impact the dissolution phenomenon and would enhance this mechanism. The study was performed on the five microbial strains used for Challenge Tests for checking the safety of pharmaceutical and cosmetic products. Microbiological tests on solid agar plate and in broth culture were performed to evaluate the antimicrobial efficacy of both ZnO particles and Zn^{2+}. This work was performed taking into consideration the dissolution of ZnO particles in aqueous media depending on the environmental conditions and on the physicochemical characteristics of ZnO powders using three different ZnO grades.

2. Materials and methods

2.1. Materials

The following ZnO powders of pharmaceutical grade were studied: ZnO-1 from Rockwood Pigments (Beltsville, US); ZnO-2 from SILOX (Engis, Belgium); ZnO-3 from Zinc Corporation of America (Pittsburgh, US). Zinc gluconate (ZnG) was supplied by Seppic (Castres, France).

2.2. ZnO particles characterization studies

The physicochemical properties of the three ZnO grades were investigated as previously reported [46]. The characteristics of the powders were assessed in a dry state by determining their specific area and the porosity by nitrogen adsorption measurements using a Tristar 3000 Micromeritics BET instrument. The specific area was determined by the Brunauer–Emmett–Teller (BET) multipoint method and the pore volume was analyzed by the Barrett–Joyner–Halenda (BJH) method. The crystal structures were established by X-ray diffraction measurements performed at the 'Centre Henri Longchambon' facility (University of Lyon) using a Bruker AXS D8 Advance X-ray diffractometer operating with the Cu Kα1 line at 1.54 Å wavelength. The crystallite size was estimated from the width at half height of the Bragg peaks using the Debye–Scherer equation. The apparent density was studied following an adapted protocol of the European Pharmacopeia. Size and shape of the elementary particles were studied by transmission electron microscopy (TEM) performed at the 'Centre Technologique des Microstructures' facility (University of Lyon) on a Philips CM120 microscope operating at 80 kV acceleration. A dilute aqueous suspension (0.1%) was spread on Formvar/carbon grids and dried before observation.

The behavior of the aggregates of ZnO particles was also evaluated in liquid media by measuring the isoelectric point by electrophoretic light scattering measurements using a Zetasizer Nano ZS (Malvern Instruments, UK). The sedimentation phenomenon was followed measuring the turbidity of the samples using a Carry 50 UV–vis absorption spectrophotometer (Varian). The turbidity τ (cm^{-1}) was deduced from the absorbance A_λ measured at a wavelength of 380 nm in a cell of optical path $l = 1$ cm according to the following equation: $\tau = 2.303\,A_\lambda/l$. Finally, the diameters of ZnO aggregates in water and in nutrient broth used in antimicrobial tests were measured by low-angle laser light scattering using a Malvern Mastersizer 2000 instrument. Agglomerate size distributions were calculated according to Mie theory using the refractive indices of water (1.33) and ZnO (2.008). The refractive index of the Mueller Hinton culture broth used for antimicrobial tests measured using a PAL-1 refractometer (Atago, France) was 1.336. The full granulometric distribution was retained as a characteristic parameter.

2.3. Evaluation of antimicrobial activity

The microbiological experiments were carried out in triplicate on the five microbial strains used for Challenge Tests of the European 7.0 and US Pharmacopeias 35 supplied by the culture collection of the Institut Pasteur (France): *Escherichia coli* CIP® 53.126 (equivalent strain ATCC® 8739); *Staphylococcus aureus* CIP® 4.83 (ATCC® 6538); *Pseudomonas aeruginosa* CIP® 82.118 (ATCC® 9027); *Candida albicans* IP 48.72 (ATCC® 10231); *Aspergillus brasiliensis* IP 1431.83 (previously named as *Aspergillus niger* ATCC® 16404). Cell cultures and incubations were performed in a thermostated chamber in the dark.

2.3.1. Preliminary experiments by the disc diffusion test

Disc diffusion susceptibility tests on Mueller-Hinton (MH2) solid agar plate (BioMérieux, France) were performed. Sterile standard discs of cellulose of 6 mm diameter (BioMérieux, France) were impregnated with antimicrobial materials and deposited on a microbial culture in agar medium. This standard method has been used for solutions of ZnG and was adapted to the particulate nature of the present materials as follows. The cellulose discs were impregnated with sterile aqueous suspensions of ZnO at 10, 50 and 100 mg g^{-1} concentrations by soaking the discs into the suspensions for 5 s. The impregnated discs were placed onto the agar surface previously inoculated by spreading the microbial suspension on the surface of the agar. After overnight incubation in the dark at 32.5 °C for the bacterial strains and 48 h at 22.5 °C for the fungal strains, zones of inhibition around each disc were observed.

2.3.2. Measurements of antimicrobial activity in liquid broth

The antimicrobial efficacy of either ZnO particles or soluble zinc species was evaluated in Mueller Hinton (MH) broth (AES Chemunex, France), a sterile medium intended for microorganisms growth. Solutions of soluble zinc species consisted of either solutions of ZnG in MH broth, or the supernatant of ZnO suspensions in MH broth obtained by centrifugation for 10 min at 5000 rpm. Suspensions of ZnO of various concentrations (from 1.25 to 80 mg g^{-1}) were prepared by dispersing the ZnO powder in MH broth for 1 h in an ultrasonic bath. A preliminary study has validated the conditions of this dispersion step [46]; in particular it has shown that dispersion by ultrasounds did not alter the intrinsic antimicrobial properties of ZnO. Each sample was inoculated with the microbial strains and incubated at the appropriate temperature (32.5 °C for bacterial strains; 22.5 °C for fungal strains). Aliquots were collected at different incubation times (24 h for bacterial strains and 48 h for fungal strains), diluted in tryptone salt broth (AES Chemunex) before seeding the suitable dilution on TSA agar plate (BioMérieux) for incubation in the dark (24 h for bacterial strains, 48 h for *C. albicans* and 72 h for *A. brasiliensis*) and counting the colonies. A 'positive control' experiment consisted of inoculation of the microbial strains in pure zinc-free MH broth.

Additional experiments on ZnO suspensions and soluble zinc species were conducted in water in place of MH broth in order to assess the influence of zinc solubilization by MH broth. These experiments were conducted according to the same method as for those in MH broth.

2.4. ZnO dissolution experiments

The dissolution of ZnO particles under different experimental conditions was examined trough separate experiments, each performed in triplicate. ZnO suspensions were prepared and homogenized in hemolysis tubes of 5 mL. For each sample, ZnO suspensions were vortexed for 10 s and a 10 min centrifugation step at 5000 rpm was applied. The supernatant was collected, filtered through a 0.20 μm regenerated cellulose syringe-filter (Uptidisc®, Interchim, Montluçon, France) and introduced in a polypropylene 1 mL vial for analysis of zinc. Every chemical was of analytical grade and solutions/suspensions were prepared with water for HPLC (resistivity of 18 MΩ cm).

2.5. Zinc ions analysis

Zinc content released from the dissolution of ZnO particles was quantified using a high-performance liquid chromatography (Waters) coupled to a detection using a post-column reaction with the 4-(2-pyridylazo)resorcinol reagent [47]. This method allows a chromatographic separation of ions that provides the selectivity of the analysis and a sensitive detection through the post-column formation of a colored complex [48]; it has already been applied to the analysis of Zn^{2+} ions in protein media [47]. Firstly, zinc ions in the supernatant were separated on a non-polar stationary phase (column X Terra MSC18-5 μm-3.9 × 150 mm, Waters) with an acid mobile phase composed of sodium octane sulfonate (0.2 mM), tartaric acid (25 mM) and acetonitrile (2%). The pH of the mobile phase was adjusted at 3.5 adding sodium hydroxide. Then, a post-column reaction took place at 50 °C with 4-(2-pyridylazo) resorcinol (PAR reagent, Sigma-Aldrich) in ammonia solution. Complexation of Zn^{2+} by the PAR reagent yielded colored complex species that were detected by means of their absorbance in the visible domain. The detection of the complex PAR-Zn^{2+} was realized with a diode array detector at a detection wavelength of 505 nm corresponding to the maximum of the absorption spectra of the red–orange complex. Acquisition and data processing were done with the software Empower Photodiode Array (PDA, Waters). The quantitative analysis of Zn^{2+} concentration was performed with help of an external calibration with zinc gluconate solution in acidic conditions ensuring a total dissociation of the zinc salt as free zinc ions.

3. Results and discussion

3.1. Antimicrobial activity of ZnO and Zn^{2+}

Preliminary experiments performed in agar medium revealed inhibition zones around ZnO impregnated discs (Fig. 1). Since ZnO particles were unable to diffuse out of the cellulose discs, antimicrobial species have necessarily been released from the ZnO impregnated discs to the agar medium. This indicated that ZnO particles were able to exhibit an antimicrobial effect by diffusion of soluble species into the agar medium. This test gave a first qualitative estimate of the sensitivity of microbial strains to ZnO particles through the contribution of released Zn^{2+}. *E. coli* and *S. aureus* were

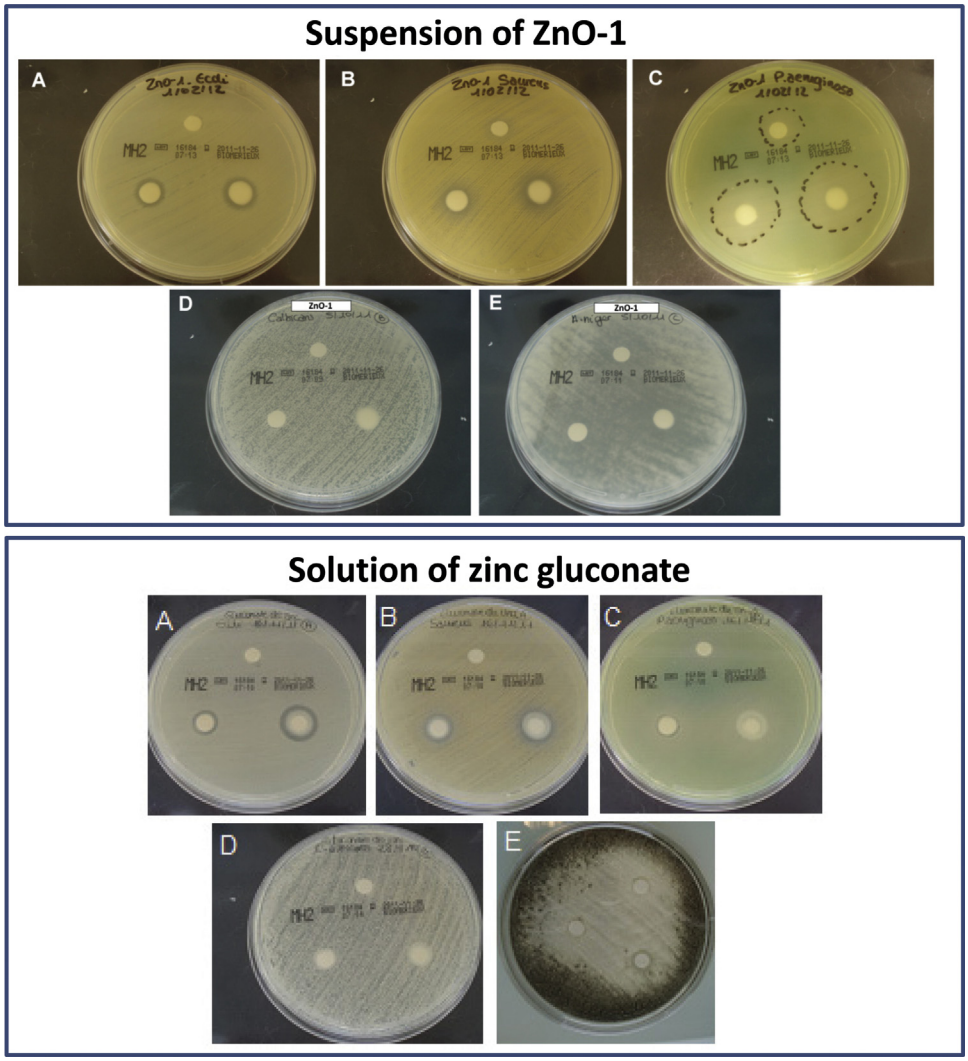

Fig. 1. Disc diffusion tests for the evaluation of antimicrobial activity of ZnO-1 (10, 50 and 100 mg g^{-1}) (top) and zinc gluconate (10, 50 and 100 mg g^{-1}) (bottom). (A) *E. coli*; (B) *S. aureus*; (C) *P. aeruginosa*; (D) *C. albicans*; (E) *A. brasiliensis*.

sensitive to soluble species since clear inhibition zones of the bacterial growth around the discs could be observed. These two bacteria were more sensitive than *P. aeruginosa* for which only a large pale green colored halo was observed. Similar results were obtained with the soluble ZnG, showing that the antimicrobial activities of the soluble zinc species were indeed at the origin of the inhibition zones. The disc diffusion test did not reveal any growth inhibition of the yeast *C. albicans*, neither by ZnO nor by ZnG. Conversely, the germination of the spores of *A. brasiliensis* was inhibited by ZnO and ZnG, the activity of ZnG being much higher. For the microbial strains on which an efficacy was proven with this test, a concentration-dependence has been noticed: the inhibition zones were larger for the highest concentrations of ZnG and ZnO. This latter result points out the impact of the dissolution phenomenon of ZnO particles into the culture broth medium.

Quantitative assessment of antimicrobial activities was done by experiments in liquid broth medium and in pure water. Various efficacy indexes were determined: the Minimum Inhibitory Concentration (MIC) and the Minimum Bactericidal Concentration (MBC) evaluated the efficacy on bacteria; an 'inhibition rate' was defined as the ratio of the population densities of the sample for 80 mg g^{-1} of ZnO to that of the positive control measured 48 h after inoculation to quantify the activity on *C. albicans*; and a visual MIC estimated as the lowest concentration of ZnO that prevented the development of mycelium 48 h after inoculation was used to measure the efficacy of ZnO on *A. brasiliensis*. Thanks to these values, ZnO grades were sorted with respect to their efficacy (Table 1): ZnO-1 exhibited the highest efficacy, whereas ZnO-3 was the less effective and ZnO-2 displayed an intermediate activity closer to ZnO-1 than ZnO-3 [46].

The antimicrobial effects of the three types of Zn-containing samples were comparatively tested in broth medium: ZnO suspensions, their supernatants and ZnG solutions. ZnG was used as a reference for soluble zinc species although zinc is not present as totally free Zn^{2+} in the solution. The use of ZnG allowed the study of high concentrations of soluble zinc that fully dissociated zinc salts such as zinc chloride or zinc acetate would not reach because of their instantaneous precipitation in the neutral or basic media. Zinc ions of ZnG are partially complexed by gluconate and complexing species contained in the MH broth. High enough concentrations of free Zn^{2+} would require an acidic pH, but the slightly basic pH of the culture broth must be retained for an optimal microbial growth. The results reported in Fig. 2 for ZnO-1 show a reduction of the microbial populations in the presence of ZnO-1suspensions, ZnO-1 supernatant, or ZnG. The comparison between ZnO suspensions and supernatant revealed that the antibacterial activity was significantly less for the soluble species alone than for ZnO-1 suspensions. The difference between the two gave the contributions

Table 1
Characteristics of the antimicrobial efficacy of ZnO particles and zinc gluconate on the five microorganisms.

Microbial strain	Raw material	ZnO-1	ZnO-2	ZnO-3	Zinc gluconate
E. coli	MIC (mg g^{-1})	1.2	2.5	12.8	1.7
	MBC (mg g^{-1})	14.4	17.2	18.1	8.4
S. aureus	MIC (mg g^{-1})	1.8	3.0	46.8	4.6
	MBC (mg g^{-1})	15.6	31.8	75.2	>80
P. aeruginosa	MIC (mg g^{-1})	23.0	34.0	57.0	33.6
	MBC (mg g^{-1})	64.0	68.1	>80	>80
C. albicans	Inhibition rate (%)	33.6	35.9	24.7	47.3
A. brasiliensis	Visual MIC (mg g^{-1})	10	20	80	<10

of the mechanisms that required the presence of ZnO particles *in situ*. The antimicrobial activity by direct contact of ZnO particles to the cell walls was absent in the experiments with the supernatant. There might be ROS present in the supernatant because they have been generated before its separation by centrifugation and remained in the state of the stable hydrogen peroxide species (H_2O_2). However, *in situ* photo-generation of the most active ROS by ZnO particles is not operative in the supernatant. As a whole, the antimicrobial activity of the supernatant mainly comes from the soluble zinc species; a slight supplementary activity may arise from residual ROS. The contribution of ROS to the antimicrobial activity of ZnO is a complex topic that deserves a full paper to be correctly addressed. A specific study will be published soon on this subject. Beyond the suppression of the direct action by close contact, the removal of ZnO powder from the media stopped any further dissolution of soluble zinc species. This part of the study demonstrated that soluble Zn^{2+} released by partial dissolution of ZnO had a definite contribution to the antimicrobial activity of ZnO. The quantification of the contribution of the soluble zinc species is difficult because the shape of the plots of Log(CFU mL^{-1}) with respect to [ZnO] (Fig. 2) are not similar for the full ZnO suspensions and their supernatants. A rough estimate was made from the slopes of the curves d(Log(CFU mL^{-1}))/d[ZnO]. For *E. coli*, the contribution of soluble zinc species was approximately 15% of the full antimicrobial activity of ZnO; it was 71% for *S. aureus*; and it finally reached almost 100% for *C. albicans* (the soluble zinc species were responsible for the full activity of ZnO). There was a definite specificity of the antimicrobial activity of the soluble zinc species with regards to the microbial strains. The behavior was more complex for *P. aeruginosa*: almost 100% of the antibacterial activity was caused by the soluble zinc species for [ZnO] < 10 mg g^{-1} and the contribution of soluble zinc species turned small for [ZnO] > 10 mg g^{-1}, because the antibacterial activity of ZnO became high above this ZnO concentration whereas the activity of the soluble zinc species did not increase significantly.

Zinc concentration has been measured in the supernatant separated by centrifugation, thus allowing the comparison of antimicrobial activities of the soluble zinc species released by ZnO particles in the MH broth and that of ZnG. Such comparison is presented in Fig. 3. The antimicrobial activity of soluble zinc species and ZnG appeared of comparable magnitude for most strains except *E. coli*. A noticeable feature of the antimicrobial activity of soluble zinc species is the weak activity at high concentrations. There were two regimes (Fig. 3): the microbial populations decreased significantly with respect to the concentration of zinc for low Zn^{2+} concentrations, and remained approximately at the same level whatever the concentration of Zn^{2+} above 1 mg g^{-1}. ZnG had a higher antimicrobial activity against *E. coli* than a similar Zn^{2+} concentration released from ZnO in the broth. Such an enhancement of antimicrobial activity by the gluconate suggests that *E. coli* is

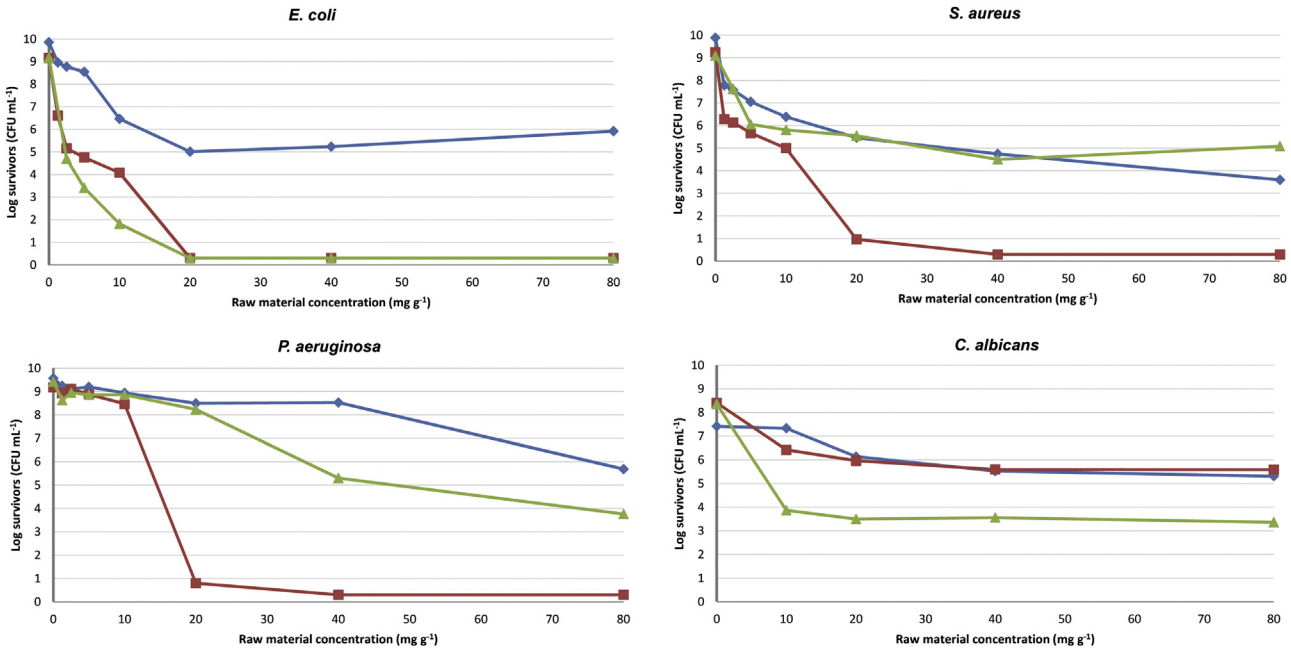

Fig. 2. Decrease of microbial populations with respect to zinc concentration for ZnO-1 suspension (red squares), its supernatant (blue diamonds), and zinc gluconate solution (green triangles). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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