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Synthesis and Antimicrobial Applications of ZnO Nanostructures: A Review

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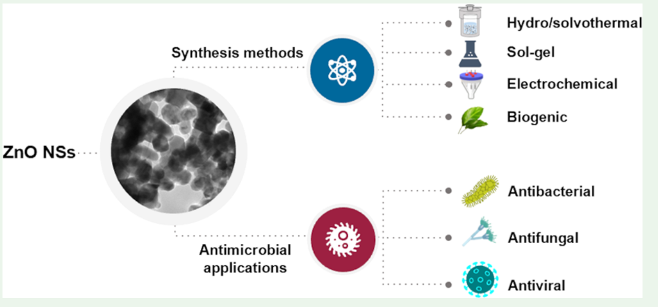

ABSTRACT: ZnO nanostructures (ZnO NSs) are able to provide significant antimicrobial activity, ensuring high biocompatibility, good chemical stability, and low toxicity. Such versatility has led to great success of this nanomaterial for antibacterial, antifungal, and, more recently, antiviral applications. However, methods for the preparation of ZnO NSs must be properly selected for their end use. Moreover, ZnO NSs can also be cytotoxic to some extent. In this context, this review emphasizes some aspects relevant to the preparation as well as to the antimicrobial use of ZnO NSs. In particular, a brief overview of the sol−gel, hydrothermal, biogenic, and electrochemical approaches proposed for their synthesis is presented, highlighting advantages/drawbacks of each route in terms of scalability, simplicity, and efficacy. Next, the application of ZnO NSs in several fields is reported. This is followed by a discussion of the antimicrobial role of ZnO NSs, where antimicrobial mechanisms of action, possible cell resistance, and cytotoxicity of ZnO NSs are highlighted. We also discuss the role of ZnO NSs against different biothreats, such as bacteria and viruses. The future of such nanomaterials in this application field is addressed in the final part.

KEYWORDS: *zinc oxide, electrochemical approach, antibacterial, antifungal, antiviral, cytotoxicity*

1. INTRODUCTION

ZnO[1] exhibits excellent optical, luminescent, and antimicrobial properties,[2,3] along with high biocompatibility, chemical stability, and reduced toxicity.[4] Searching for literature within Scopus[5] from 2015 on, it was possible to select over 100 reviews and 12,000 articles dealing with ZnO nanostructures (ZnO NSs). ZnO gained great popularity in the past decade, becoming the third most commonly used metal-containing nanomaterial.[6] In particular, nanosized ZnO has been proven effective against both Gram-positive and Gram-negative bacteria,[7] fungi,[8] and viruses,[9] being useful to overcome the overutilization of antiseptics and antibiotics to combat the threat of uncontrollable infections and multidrug-resistant (MDR) microbe transmission.[10] In fact, today the problem of antimicrobial resistance (AMR), which accounts for the spreading of bacteria/fungi insensitive to antibiotics/antifungals, caused 1.27 million deaths worldwide in 2019.[11] The six leading pathogens for deaths associated with resistance are *Escherichia coli*, followed by *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.[11] Interestingly, some studies have shown that ZnO NSs can be effective against resistant species.[12,13] Additionally, compared with other metal nanomaterials, ZnO NSs are relatively less toxic and reasonably inexpensive.[14,15] Moreover, ZnO has been defined as a Generally Recognized As Safe (GRAS) material by the U.S. Food and Drug Administration (FDA).[16] In this sense, it has been used against food pathogens including *Listeria monocytogenes*, *Salmonella enteritidis*, *Bacillus cereus*, and *Pseudomonas* spp.[17] Recently, anti-inflammatory, anticancer, and antioxidant properties have also been addressed.[14,15] ZnO (nano)materials, indeed, are often used in ointments, creams, sunscreens, etc., as the most common ingredient in personal care products. Due to their strong antimicrobial effect,[6,18] ZnO-based commercial products[19] comprehend wound dressings (e.g., diabetic socks, Pishran Nassaji Ayandeh, Iran), dental fillers and toothpastes, antiacne beauty creams (e.g., 3M Touchless Care, USA; Dr. Bauman Zinc Cream, Germany), and smart food packaging (e.g., polypropylene or polyethylene or polycarbonate masterbatch with ZnO, Taban Andish Berjis, Iran; polypropylene granule, Rangdaneh sirjan, Iran), just to cite a few. The success for the use of these NSs is due to the UV filtration in sunscreens and skin creams, the antiplaque and antimalodor

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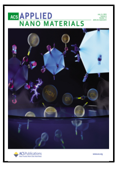

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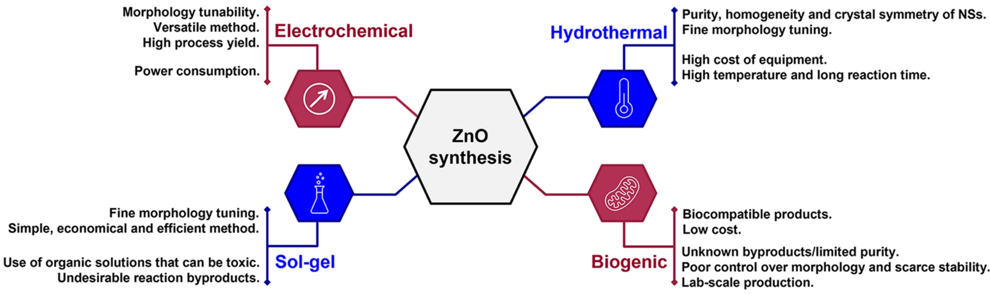

Figure 1. Comparison of the main synthesis methods used for ZnO NSs production. Their advantages and disadvantages are highlighted, especially in terms of sustainability and efficacy.

benefits for the oral products, and the biocidal effect on bacteria (Gram-positive and Gram-negative), fungi, and algae, which could favor wound healing.[20,21] The most common processes proposed for the synthesis of ZnO NSs are sol–gel, hydro/solvothermal, and biological routes. Moreover, electrochemical synthesis can be also employed to prepare ZnO nanomaterials[22] and is proving to be a suitable alternative method in terms of sustainability and scalability. Figure 1 provides an overview of the main synthesis features, which are better discussed in the following section. As will be discussed in the following, each of them has different peculiar aspects, e.g., tunability of sizes and shapes, purity and homogeneity, potential toxic byproducts, and scalability of the process. For this reason, the choice of the proper synthesis is crucial for the final application of ZnO NSs. In the second part of the review, an outline of the main antimicrobial applications is reported, followed by a concluding discussion on challenges and potentialities of the use of ZnO NSs in real-life products.

2. PROCESSES FOR THE SYNTHESIS OF ZNO NSS

Each synthetic route to ZnO NSs presents specific tunable parameters, which in turn affect NS physicochemical properties. It is expected that the nanoparticle morphology, surface area, surface charge, solubility, and degree of aggregation will strongly influence, for example, the availability of active sites for photocatalysis, the extent to which zinc cations can be released to exert antimicrobial action, and so on.[23] Hydrothermal and sol–gel routes are the most prone to the development of ZnO NSs with different morphologies by proper selection of stabilizers and/or solvents.[24,25] A recent review by Raha and Ahmaruzzaman[26] thoroughly described the role of synthesis parameters on ZnO NSs morphology. However, many studies have already demonstrated that size and concentration of NSs influence the antibacterial activity more than the morphology does.[15,27−30] On the other hand, the antifungal and antiviral properties of elongated ZnO NSs seem more pronounced[31−33] (*vide infra*). In the following paragraphs, four synthetic routes to ZnO NSs are reported with specific attention to the final application of the produced NSs as antimicrobial agents.

2.1. Sol–Gel Syntheses. The sol–gel approach is a bottom-up process that has often been recognized as the method of election for metal oxide nanomaterials. In particular, it allows preparation of very small ZnO nanoclusters on the order of a few nanometers.[34] This holds true because of easy formation of polymeric hydroxides,[25] which means that Zn hydroxyl complexes can polymerize by forming Zn−O−Zn bridges with final transformation into ZnO. In the conventional setup, first the hydrolysis of the precursor solution occurs, followed by condensation, resulting in the gel formation. Afterwards, different steps involving aging, solvent extraction, and thermal treatment are carried out to prepare the desired nanostructures. The main advantages of the method reside in the ability to fine-tune the morphology and size. In this respect, Figure 2 clearly shows how the synthesis

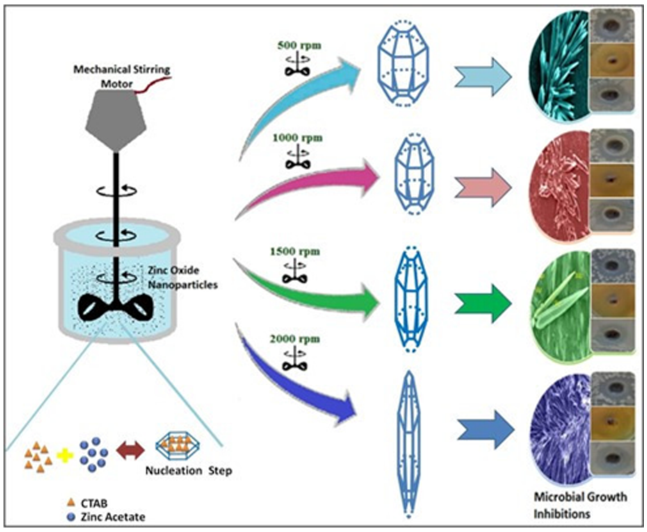

Figure 2. Schematic illustration of a sol–gel route, which provides thornlike ZnO nanoparticles according to different mechanical stirring conditions. From ref 35. CC BY 4.0.

parameters, such as the mechanical stirring conditions, are able to affect the final NS features.[35] Organometallic zinc precursors (zinc acetate dihydrate, zinc acetylacetonate hydrate, zinc 2-ethylhexanoate, etc.)[34,36,37] and organic solvents (ethanol, 2-propanol, methanol)[25,38] are often employed. Alternatively, inorganic zinc salts have been used as well.[39] However, the presence of alcohols and a strict control of pH are typically needed to produce ZnO NSs with high purity.[25,38,40] It has been reported that the Zn^{2+}/OH^{-} ratio, temperature, and alcohol chain length are critical parameters to control ZnO NS growth.[41] Additional coadjutants are typically present in the reported sol–gel protocols, either to improve the process yield or control the morphology.[25,40,42] A proper choice of the solvent mixture can lead also to different shapes.[39] In many cases, refluxing and distillation steps are needed to remove reaction byproducts, and calcination treatments are also involved to obtain the final nanopowders.[25,38] Sol–gel methods are versatile and reliable. They offer an almost quantitative process yield,[34,39] though the majority of the

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works report only a rough estimation. Major drawbacks may reside in the need for careful control of synthesis parameters and the intrinsic sensitivity to reaction condition, which may limit their industrial potential,[25,43] the presence of reaction byproducts, the need for additional postreaction treatments, and the overall process time. On one hand, sol−gel routes are competitive with physical methods in terms of lower processing temperatures, lower costs, and scalability,[39] providing ZnO NSs with reproducible morphology and size homogeneity;[25,26,38] on the other hand, some reagents and byproducts can be toxic for both humans and the environment, limiting the sustainability of these routes. Moreover, long reaction times and high calcination/annealing temperatures can lead to energetic processes with increased costs compared to those of the other chemical methods presented here.

2.2. Hydro/Solvothermal Syntheses. Among all the ZnO bottom-up synthesis methods, the hydrothermal technique[44] occupies a primary place due to its advantages over conventional technologies, especially with regard to homogeneity and crystallinity of nanostructures. In a typical hydrothermal synthesis, all reagents (metal oxide precursors, possible stabilizers, solvents) are mixed together, introduced into a Teflon-lined stainless steel autoclave, and heated. As a result of controlled temperature and pressure, high product purity and homogeneity, crystal symmetry, narrow particle size distribution, and morphology control are ensured.[45] The hydrothermal method was applied to synthesize a variety of ZnO NSs. One of the first works was published in 1990 by Chittofrati and Matijević,[46] who demonstrated that the resulting shape of as-synthesized NSs was strongly dependent on the nature of the added base. They suggested that the shape of ZnO structures is affected by the nature of zinc ion solute complexes, which differs depending on the base cation used (LiOH, NaOH, or KOH).[46]

The temperature and pressure values as well as the synthesis time and the used reagents are the main parameters affecting the characteristics of the final products. The hydrothermal methods allow specific control of them, providing suitable routes for the production of specific nanostructures[24] according to their technological application. Lu and Yeh synthesized ellipsoidal ZnO nanoparticles in ammonia alkaline medium, highlighting the importance of controlling the pH of the system during the nucleation and growth of ZnO NSs,[47] rather than the reaction time. Similar findings were reported by Chen et al., who proposed also the use of different additives to explore different morphologies, such as rodlike, spindlelike, and sheetlike, in the size range of 100−500 nm.[48] Evidences that the acidity of the medium affects the directional growth in ZnO nanocrystals were also reported,[49] acting on both nucleation kinetics and amount of primary seeds. Besides the conventional hydrothermal route with aqueous solvent in the system, similar methods have been developed, such as the solvothermal (with nonaqueous solvent) and supercritical hydrothermal (either aqueous or nonaqueous under supercritical conditions) processes. Wang and colleagues compared ZnO NSs synthesized by hydrothermal and solvothermal methods, assisted by cetyltrimethylammonium bromide (CTAB). They observed that the used solvent, water or ethanol specifically, induced different morphologies, ranging from nanoflowers to nanorods, hexagonal crystals, and small microspheres.[50] Attractive studies have proposed hydrothermal synthesis using supercritical water.[51] For instance, ZnO NSs were synthesized using a flow-type apparatus for rapid heating of zinc nitrate and potassium hydroxide aqueous solution to supercritical conditions (30 MPa, temperatures ranging from 573 to 673 K).[52] The supercritical conditions allow control of the hydrothermal reaction rate and, as a result, the particle size, morphology, and crystal structure. As mentioned before, the main advantage of hydrothermal synthesis is the fine control of morphology and crystallinity of ZnO nanostructures.[26] A wide variety of nanomaterials have been presented over time: porous nanotubes with nanoscale holes,[53] monodispersed ZnO nanorods with diameter of 50 nm,[54] etc. Some of them are reported in Figure 3. In addition, the hydrothermal method usually ensures a high yield of the ZnO NS production, which can range from 60% to 90%, according to the synthesis conditions.[47] However, the relatively high cost of equipment, the high energy consumption, and the inability to observe the reaction process in the autoclave are well-known issues of hydrothermal/solvothermal synthesis.[55,56] In addition, the longer synthesis time may be considered a limit to process sustainability and scalability. The use of organic solvents for the solvothermal processes adds further environmental concerns as well. However, this route typically guarantees a catalyst-free growth of NSs and a large-area uniform production as compared with sol−gel approaches.[26]

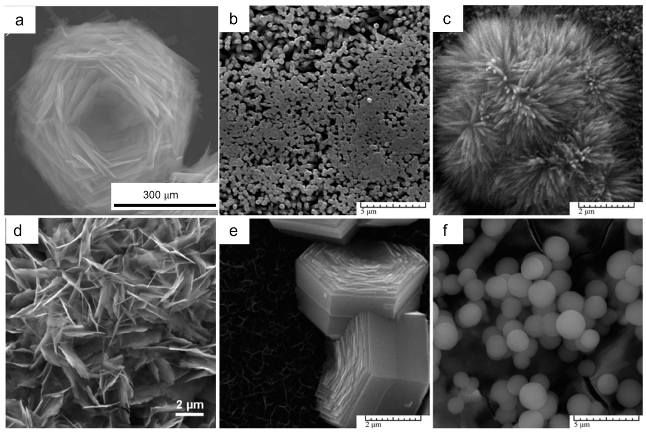

Figure 3. (a) FE-SEM images of $Zn_5(CO_3)_2(OH)_6$ precursor and nestlike ZnO hierarchically porous structures. Reproduced from ref 57. Copyright 2012 American Chemical Society. (b−f) SEM images of ZnO nanostructures synthesized in the presence of capping agents: (b) control sample without agents; (c) after addition of polyethylenimine; (d) after addition of urea; (e, f) after addition of sodium citrate at 5 and 10 mM. Adapted with permission from ref 24. Copyright 2020 Royal Society of Chemistry.

2.3. Biogenic Syntheses. The biosynthesis of ZnO NSs has been proposed, mostly in the last 15 years, as a cheap and environmentally friendly bottom-up option to chemical and physical methods.[58] Many applications of phytogenic ZnO NSs have been recently reviewed by Prasad et al:[59] thanks to their intrinsic biocompatibility, biogenic ZnO NSs have been extensively studied for their biological applications and environmental remediation. Many plant extracts contain a large amount of phytochemicals, which can act both as reducing and stabilizing agents.[60] The use of plants and plant-derived substances was found to lessen remarkably the requirement of expensive chemicals with limited availability and hazardous experimental protocols.[61] ZnO NS production from plant extracts[62,63] is in principle easily scalable and then highly appealing for industrial and technological use.

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Furthermore, this approach is extremely straightforward. Briefly, a zinc salt (mainly zinc nitrate, chloride, or acetate) is added to a plant extract; after a proper reaction time (catalyzed, when appropriate, by sunlight or other energy sources), the produced suspension is washed and subjected to thermal treatments to produce stoichiometric ZnO nanopowders[64,65] (Figure 4). This indicates that these routes also require additional steps to obtain the final product. An interesting review on phytogenic ZnO NSs was recently published.[66] A plethora of plants, flowers, and extracts have been proposed to achieve the green synthesis of ZnO NSs. An exhaustive list of these methods goes beyond the aim of this review. However, it is worth mentioning that the final choice of a certain plant is generally dictated by the local flora, i.e., from the availability of some vegetable species in specific regions. Based on the peculiar composition of each plant extract, different shapes of ZnO NSs were obtained, ranging from spheroidal particles (which are most common), to rodlike and flowerlike ones.[67] However, the control over purity and quality of the final ZnO NSs, especially in terms of size and morphology, can be difficult to achieve because of limited control of the active species in the case of plant-mediated synthetic routes.

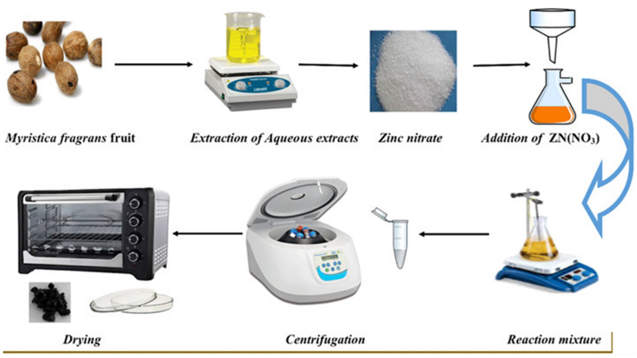

Figure 4. Schematic procedure for the biogenic synthesis of ZnO NSs. From ref 65. CC BY-NC-ND 4.0.

Similar considerations apply to other biogenic syntheses employing seaweeds and cellular algae to prepare ZnO NSs, useful as active layer for the preservation of seafoods.[68] Another class of biomediated syntheses relies on the use of food wastes and herbs. Among them, edible vegetables and nuts contain terpenoids, polysaccharides, and aromas with both reducing and stabilizing properties.[69] Only during the last year, many different examples have appeared in literature, ranging from fruits peels to olives[70] and oranges.[71] A wide variety of herbs have been used for the same aim. In this case, odorous molecules can play the role of reductants and stabilizing agents for ZnO NSs. These NSs are widely used as food-preserving packaging to extend the shelf life of perishable foods; some examples have been recently published about guava fruit[72] and ichthyic products.[73] Bacteria-mediated synthesis of ZnO NSs is less common. In this case, the metal precursor should be added to a bacterial culture in the planktonic state. Enzymes and proteins exert the reducing action.[67] The tentative mechanism for production of NSs by this approach has been reviewed in several works.[60,66] As metal NSs have a certain antimicrobial action, it is necessary to use metal-tolerant[74] and thermophilic[75] bacterial strains. Although a substantial amount of research has been published in this field, the mechanism behind the formation of ZnO NSs during these syntheses still needs to be defined. In fact, the complex and variable nature of reaction media makes the amount of possible reactions extremely wide.[59,76] Indeed, an extensive variety of biological substrates with distinct compositions have been applied for this purpose. Concentration of zinc salts, pH variations, reaction times, and temperatures can vary considerably among proposed synthetic approaches, resulting in particles with diverse sizes and morphologies. As an example, it was demonstrated that the higher the reaction temperature, the higher is the average NS size due to faster crystal growth.[77] A detailed discussion on how experimental parameters and chemical nature of bioreductants can affect ZnO NS morphology, chemical properties, and applications was published by Bandeira et al.[61] It is worth pointing out that biogenic procedures may also have some drawbacks. In a recent review, both advantages and disadvantages of biosynthesis versus conventional routes were addressed.[78] The main advantage is the "green character" of the approach in terms of recyclable sources and low-toxicity solvents; however, the high batch-to-batch variability of synthesized NSs, limited process reproducibility, and unpredictable scalability are limiting factors for these methods.[78] Moreover, in most cases, the exact biochemical composition of the reaction mixture is unknown; hence, it is not possible to foresee which byproducts and wastes could be developed during the process.[79] Finally, some of these synthetic protocols could need a large amount of solvent (water, in most cases) for obtaining phytoextracts with a non-negligible environmental impact.[78]

2.4. Electrochemical Approach. The need for alternative routes for the synthesis of nanomaterials have led different research groups to investigate electrochemical methods.[22,23,80] In fact, aqueous or hydroalcoholic media are typically employed in the electrosynthesis of ZnO NSs[23,81] with different morphology and size. In contrast to the other methods mentioned above, an advantage of electrosynthesis resides in the use of a solid precursor, namely, a zinc electrode, that is oxidized under controlled conditions.[81] In other words, a sacrificial anode is used as a source of zinc cations in a top-down approach. Though this approach arose in the late 1990s, only in the last 10 years has it gained popularity and has been further developed for the preparation of NSs in different laboratories. Mandler and collaborators developed an appealing strategy known as electrochemical sol−gel.[82,83] Protic solvents can be electrolyzed with consequent generation of OH^- ions, causing a local variation of pH near the electrode, which in turn induces the sol−gel condensation. According to this route, electrochemical parameters can trigger localized pH or ionic strength change promoting the production of nanostructured metal oxides/hydroxides from their precursors[84] or from nano-objects.[85] The works by Chandrappa et al.[86,87] introduced a two-step method capable in principle of large-scale synthesis of ZnO NSs. The approach is based on low current densities and uses a well-known corrosive species for zinc: hydrogen carbonate. In fact, solutions containing carbonate ions promote a dissolution/passivation process of zinc surfaces, as reported in classical electrochemical studies.[88] A second step, implying a thermal treatment above 300 °C, guarantees the full conversion of the electroproduced nanostructured gels (mainly made of alkaline zinc carbonate, $Zn_x(CO_3)_y(OH)_z$) to pure ZnO NSs. In 2015, we studied the combination of the sacrificial zinc electrolysis in sodium hydrogen carbonate solution (30 mM) with typical strategies

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applied in sol−gel routes to achieve morphological control.[89] This modification offered significant advantages in terms of process yield and quality of the final nanopowders. In our study, a nontoxic anionic stabilizer, poly(sodium 4-styrenesulfonate) (PSS), was employed, allowing the formation of spherical NSs with an average diameter of 15−20 nm in the gel-like state (Figure 5a). The generation of OH^- leads to the constant increase of solution pH, up to 11−12. The use of diluted $NaHCO_3$ solutions in combination with PSS was particularly effective in slowing down the anode passivation, thus extending the electrolysis duration and zinc corrosion yield.[89] Thermal annealing was essential for full conversion to ZnO NSs. Above 300 °C, spherical ZnO NSs were produced, and at 600 °C, wurtzite-phase ZnO NSs with a mean core diameter of 46 ± 8 nm were typically formed (Figure 5b). Thermal treatment reduced the possible presence of contaminants and byproducts. The need for tuning the morphology of ZnO NSs led us to the use of other stabilizers, demonstrating the versatility of this approach. In particular, we evaluated cationic capping agents capable of driving more specifically the NS growth toward elongated structures. In this sense, poly(diallyldimethylammonium chloride) (PDDA) was tested as a typical polyelectrolyte used for biosensor development and bioelectronics.[90] A milder thermal treatment (120 °C) was suitable to produce PDDA@ZnO NSs (Figure 5c). Elongated ZnO NSs (200−500 nm in length) were obtained with PDDA through a lamellar superimposition growth mechanism.

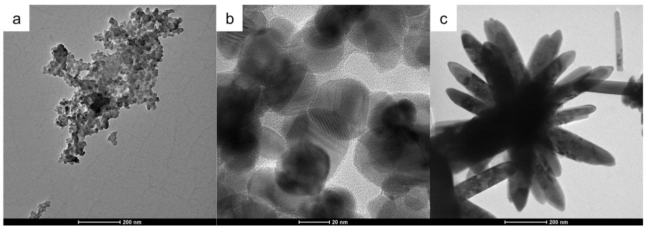

Figure 5. TEM micrographs of (a) electrosynthesized pristine nanogels prepared with 1 g/L PSS in 30 mM $NaHCO_3$ and (b) ZnO NSs after calcination at 600 °C. Reproduced with permission from ref 89. Copyright 2015 Elsevier. (c) TEM image of electrosynthesized ZnO NSs prepared with 1 g/L PDDA PSS in 30 mM $NaHCO_3$, dried at 120 °C. From ref 90. CC BY 4.0.

The need for more efficient synthetic processes in nanomaterial development has led to the coupling of multiple techniques for their preparation.[91] For example, microwaves[92] or even microplasmas[93] have been proposed to enhance electrochemical processes, providing both high-temperature reaction conditions (generated locally at the electrode−solution interface) and fast transient changes in temperature when microwave pulses are applied.[92] A successful example is also provided by the combination of sonochemistry and electrochemistry. The variety of induced effects on electrochemistry processes by ultrasound waves can be attributed to the generation, growth, and collapse of microbubbles in the electrolyte.[94,95] In the past decade, the expansion of sonoelectrochemistry has become increasingly important, considering that it allows the preparation of metal and semiconductor/alloy NSs and polymeric nanoparticles as well as nanocomposites. The ultrasonic-assisted electrochemical method was applied to improve the production of ZnO NSs. Hajnorouzi et al. proved that the electrochemical synthesis of ZnO NSs occurred 10 times faster with ultrasound, suggesting that bubbles accelerate crystal nucleation.[96] Alternatively, Zn(II) complex precursors of ZnO NSs can be prepared by sonoelectrochemical methods.[97,98] Appropriate current density and ultrasonic irradiation affect the Zn(II) complex particle size, which in turn influences the final size and morphology of ZnO nanoparticles. As a result, the synthesis of quite sophisticated nanomaterials is possible through careful control of the applied current density, ultrasound pulse, and choice of precursors.[99]

Microplasmas are particularly promising for generating advanced nanomaterials, taking advantage of being operated in synergy with other fabrication routes such as the electrochemical ones.[100,101] Microplasma was used to assist the electrochemical production of ZnO NSs. Compared with the conventional electrochemical method, this technique works with a low operating power at room temperature and atmospheric pressure.[93] Hexagonal ZnO nanosheets were prepared in the presence of sodium dodecyl sulfate (SDS) (Figure 6), exhibiting high antimicrobial activity against Gram-positive and Gram-negative bacteria (e.g., *S. aureus* and *Serratia marcescens*).[93] In the field of electrochemical synergistic strategies, the choice of suitable, nonconventional electrolytic media may greatly improve the process sustainability. For example, ionic liquids (ILs) and deep eutectic solvents (DESs)[102] are often reported as alternative baths in the electrochemical corrosion processes of Zn sheets[103] or with Zn(II) precursors[104] for the synthesis of ZnO nanomaterials. Those examples are not exhaustive of the literature but offer the reader some tools for exploring novel electrochemical methods for ZnO NS development. To summarize, electrochemical processes are rather easy, potentially scalable, and environmentally benign thanks to the limited use of precursors, and they can be carried out at ambient conditions (temperature, pressure).[105] The final properties of materials can be tuned by varying the current density and the electrochemical

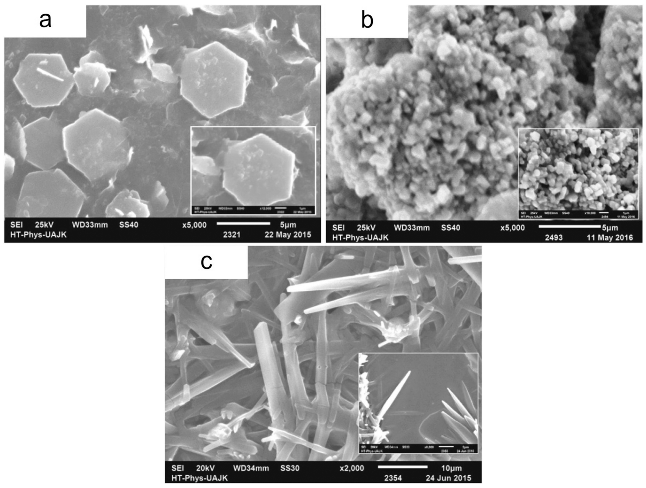

Figure 6. ZnO nanostructures synthesized at different conditions, evaluating the effect of ionic surfactants and nonionic fructose on the ZnO morphology: (a) nanosheets with SDS, (b) nanodrums with fructose, and (c) nanoneedles with CTAB, with average crystallite sizes of 40.3, 44, and 49.6 nm, respectively. The average crystallite size was estimated by the Debye−Scherrer formula on the basis of the XRD patterns. Reproduced with permission from ref 93. Copyright 2017 Elsevier.

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Table 1. Syntheses of ZnO NSs and Their Intended Application

synthesis method	reagents	temp. (°C)	time (h)	calcination	morphology	size (nm)	application	ref(s)
hydrothermal synthesis	$Zn(NO_3)_2·6H_2O$, CTAB, NaOH	150	16	500 °C, 2 h	nanoparticles, nanoplates, nanoflowers	30−80	gas sensing	109
wet chemical synthesis	$Zn(NO_3)_2·6H_2O$, L-(+)-tartaric acid, glucose, acrylamide, *N*,*N*′-ethylene diacrylamide	90	–	650 °C, 5 h	nanoparticles	80	photocatalytic activity	110
continuous hydrothermal flow synthesis	$Zn(NO_3)_2·6H_2O$, KOH	–	–	–	nanorods, nanoprisms	several tens	gas sensing	111
wet chemical method	$Zn(CH_3COO)_2·2H_2O$ in DMSO, $(CH_3)_4NOH·5H_2O$	RT	–	–	quantum dots	2.5−4.5	gas sensing	112
sol−gel method	$ZnCl_2$, SDS	RT	2	200 °C, 3 h	quantum dot	4.5	gas sensing	113
hydrothermal synthesis	$Zn(NO_3)_2·6H_2O$, trisodium citrate	200	10	–	irregular nanoparticles	100−150	gas sensing	114
solvothermal synthesis	$Zn(CH_3COO)_2·2H_2O$, benzylamine	180	24	–	nanopyramids	∼100	gas sensing	115
sol−gel synthesis	$Zn(NO_3)_2·6H_2O$, starch	90	3	600 °C, 4 h	nanoparticles	–	photocatalytic degradation	116
biogenic synthesis	banana peel extract, $Zn(CH_3COO)_2·2H_2O$	RT	3	–	nanoparticles	20−90	photocatalytic degradation	117
biogenic synthesis	*Lantana camera* plants, $Zn(NO_3)_2·6H_2O$	–	–	500 °C	nanoparticles	–	photocatalytic, electrochemical, and anti-inflammatory applications	118
biogenic synthesis	*B. cereus*, $ZnSO_4·7H_2O$	80	0.25	–	nanoparticles	20−35	antibacterial activity	119
biogenic synthesis	algae extract, $Zn(CH_3COO)_2·2H_2O$	80	3	600 °C, 2 h	nanoparticles	20−40	antibacterial, antioxidant, and hemolytic activity	120
electrochemical synthesis	$NaHCO_3$, PSS	RT	1	600 °C, 1 h	nanoparticles	∼50	OFETs, biosensors	89, 121
electrochemical synthesis	$NaHCO_3$, PDDA, PSS	80, RT	1	450−600 °C, 1 h	nanorods, nanoflowers, nanoparticles	50−500	antimicrobial applications	90, 122−124
electrochemical synthesis	$NaHCO_3$	RT	1	60−600 °C, 1 h	nanoparticles	20−70	photocatalytic activity	87

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Table 2. Representative Reviews of the Main Applications of ZnO-Based Nanomaterials in Different Technology Fields (NPs = Nanoparticles)

application field	uses	ZnO-based nanomaterials	ref(s)
agriculture and food industry	nanofertilizers	ZnO NPs	125−127
	food packaging	ZnO NSs, polymer−ZnO nanocomposites	17, 128−134
	antimicrobial agent and UV absorber in wood industry	ZnO NPs	135
	feed additives	ZnO NSs, polymer−metal oxide NPs	136, 137
biomedicine	cancer theragnostic and therapy	ZnO NPs	138−143
	biosensors	ZnO NSs, porphyrin-functionalized ZnO NSs	144−146
	fingermark sensors	ZnO and metal oxide NPs	147
	dentistry	ZnO NPs	148, 149
	antimicrobial and self-cleaning applications	ZnO and multimetal oxide NPs, ZnO NPs in textiles and polymers	140, 141, 150−159
	drug delivery	ZnO NPs, biosynthesized ZnO nanomaterials	127, 140, 141, 157, 160
	bioimaging	ZnO NPs	141, 142, 154, 160
	pharmaceutical and cosmetic applications	ZnO NPs	160, 161
	wound healing	ZnO NPs	158, 162
environment	gas sensors	ZnO NSs, porphyrin-functionalized ZnO NSs	144, 145, 163, 164
	UV sensors	ZnO nanostructures	165, 166
	adsorbent and photocatalyst	ZnO NSs, ZnO-based nanocomposites	130, 153, 156, 167, 168
	dye/organic pollutant degradation	ZnO-based nanomaterials	169−172
energy	supercapacitors	ZnO-based composites	130, 173, 174
	nanogenerators	ZnO NSs	145, 175
	flexible functional devices	ZnO nanomaterials	176
	solar water splitting	ZnO nanomaterials	177
engineering	tribological applications	polymer−metal oxide nanocomposite	178
	asphalt cement rheology	ZnO NPs	179
nanophotonics	quantum photonics and optical cavities	ZnO NPs	180
water treatment	water disinfection	ZnO NPs	181
	wastewater treatments (adsorbent, photocatalyst)	ZnO NPs	104, 182−184

bath composition.[106] Products are typically highly pure and can be isolated easily.[106] Furthermore, the experimental setup has a limited cost.[106] However, electrochemical routes require more skilled personnel and power consumption compared with the other methods.

3. APPLICATIONS OF ZNO NSS

Physical, chemical, and biological methods have been exploited to obtain different shapes and purities; in particular, it is possible to tune the size distribution and some physical properties, such as surface charge, surface area, and ZnO ζ potential, by changing the synthetic methodology. Table 1 reports a demonstrative comparison between the above-mentioned synthesis approaches and the respective features of ZnO NSs, proving their tunability according to the final applications. For the interested reader, there are several reports on the synthesis-dependent applications of ZnO nanostructures.[25,107,108]

Considering the role of ZnO NSs, it is not possible to include all of the applications in a single work. However, we wanted to provide a general overview about the wide variety of technological fields where nanostructured ZnO is used by collecting some published reviews about its application in Table 2. ZnO NSs can work as supplement, nutrient fortifier, and agricultural fertilizer due to their ability to enhance the bioavailability of Zn^{2+}, improving various biological functions including cell division, cell growth, immune function, and slow release of fertilizers. In addition, they can be suitable in the biomedicine field for the development of innovative therapy, as drug carriers, and for the enhancement of detection limits of biosensors. Furthermore, ZnO nanostructures demonstrated their efficacy in the photocatalytic activities for pollutant degradation and water remediation as well as in the energy storage. Among all the diverse features, one of the most renowned abilities of ZnO materials is killing a wide range of microorganisms, providing plenty of antimicrobial uses. In the following section such applications are faced in detail.

4. ANTIMICROBIAL APPLICATIONS

Zinc is an essential element for humans, playing a vital role in many physiological pathways, such as bone metabolism, antioxidative processes, blood clotting, enzyme activation for protein and nucleic acid synthesis and digestion.[143] However, Zn^{2+} ions can show toxicity effects if their concentration exceeds their physiological conditions. In particular, homeostasis processes regulate zinc uptake by cells, but they do not control zinc adsorption to cell membranes.[185] Therefore, the rise of Zn^{2+} concentration above optimal levels (typically between 10^{-7} and 10^{-5} M depending on the microbial strain[186]) 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.[185,187] For those reasons, Zn^{2+} ions exhibit an antimicrobial activity and can act as an antibacterial and antifungal agent. Similarly, ZnO NSs are also biocompatible and highly stable under physiological conditions. Nevertheless, at slightly acidic pH values, they undergo

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a rapid dissolution into Zn^{2+} ions, leading to the production of reactive oxygen species (ROS) and altering the metabolic and enzymatic processes. In this sense, it is widely recognized that Zn^{2+} release in aqueous media is the first proposed antimicrobial (both antibacterial and antifungal) mechanism for nanostructured ZnO.[154,185,188−190] Additional processes include the direct contact of ZnO NSs with the cell walls by electrostatic interactions, causing the destabilization of microbial membranes,[154,185,189,190] as well as ROS generation (especially hydroxyl radicals), which is enhanced under light exposure, due to the well-known photocatalytic activity of ZnO nanomaterials.[154,185,188,189,191] More details about the antibacterial and antifungal mechanisms of ZnO NSs can be found in some recent reviews.[188−190] Figure 7 summarizes the main pathways of the antimicrobial activity of ZnO materials.[192]

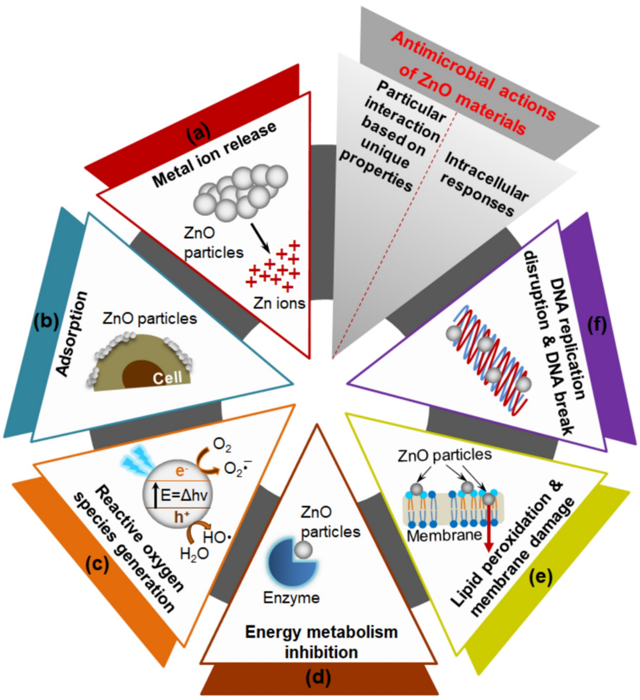

Figure 7. Mechanisms of zinc oxide (ZnO) materials used in antimicrobial applications: (a−c) particular interactions of (a) metal ion release, (b) adsorption, and (c) reactive oxygen species generation based on their physicochemical properties and (d−f) following intracellular responses of (d) energy metabolism inhibition, (e) lipid peroxidation and membrane damage, and (f) DNA replication disruption and DNA breakage. From ref 192. CC BY 4.0.

Antimicrobial efficacy of ZnO NSs is dependent on their size and surface area. In fact, these two structural parameters can influence both the kinetic/entity of ionic release and the ROS production in solution.[30]

One of the first systematic assessments of the correlation between the average size of ZnO NSs and their antibacterial activity was published 12 years ago.[193] In this interesting study, ZnO NSs of seven different sizes were tested against Gram-negative and Gram-positive bacteria, showing that smaller NS sizes corresponded to higher bacterial inhibitions.

Lallo da Silva et al.[28] showed that small, spherical ZnO NSs (around 5 nm) were able to form holes in the cell wall of *S. aureus*, as demonstrated by scanning electron microscopy (SEM) after contact between the bacteria and ZnO NSs.

As also recently reviewed,[33] the role of shape seems less important. However, it has been reported that the antibacterial activity against *E. coli* and *S. aureus* decreases following the order of flowerlike > spherical > rodlike ZnO NSs.[33,194] This is dramatically true when UV irradiation of ZnO NSs is used, due to the so-called "point effect" which strengthens ROS catalytic production.[195] The same authors, however, attributed their findings more to size and surface area than to particle morphology.[194,195]

A recent review on the mechanism of action of antimicrobial ZnO NSs and corresponding size effects was published by Gudkov et al.[32]

The use of ZnO NSs as antimicrobial agents has been known for a long time in different application fields, including bioactive nanocomposite coatings for touching surfaces and food packaging,[156,196] wound healing,[162] prevention of caries,[149] and bonelike material and implant improvement.[197] Through a bibliometric analysis based on the keywords "zinc oxide nanoparticles" and "antimicrobial", more than 8000 papers through March 2023 were collected from the Scopus database (Figure 8).[5] More specifically, by replacing the

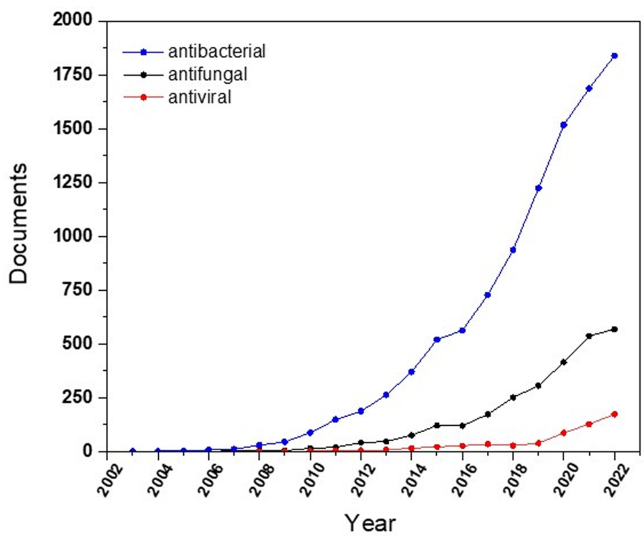

Figure 8. Annual growth of publications on zinc oxide antimicrobial applications. The works were collected from the Scopus database (Elsevier B.V.) from 2003 to 2022.

keyword "antimicrobial" with "antibacterial" or "antifungal" or "antiviral", it is evident that antibacterial applications take the lead. However, the COVID-19 pandemic emergence has boosted dramatically the interest toward antiviral applications in the last 3 years. In the following paragraphs, some relevant applications in each specific subfield are reported. It should be emphasized, however, that even though ZnO NSs have been shown to be more toxic to bacteria than to eukaryotic cells, their extensive distribution and accumulation over time predicts that the same mechanisms responsible for their efficacy against bacteria may also be responsible for potential adverse effects.[198] In particular, it was demonstrated that, similarly to dissolved Zn, ZnO NS concentrations above 50 ppm are cytotoxic and genotoxic due to the enhancement of oxidative stress induced by ROS generation.[199] Definitely, both Zn excess and scarcity undermine the loose equilibrium toward prooxidant, proinflammatory, and proapoptotic actions.[200] Such aspects are briefly commented on in the final section.

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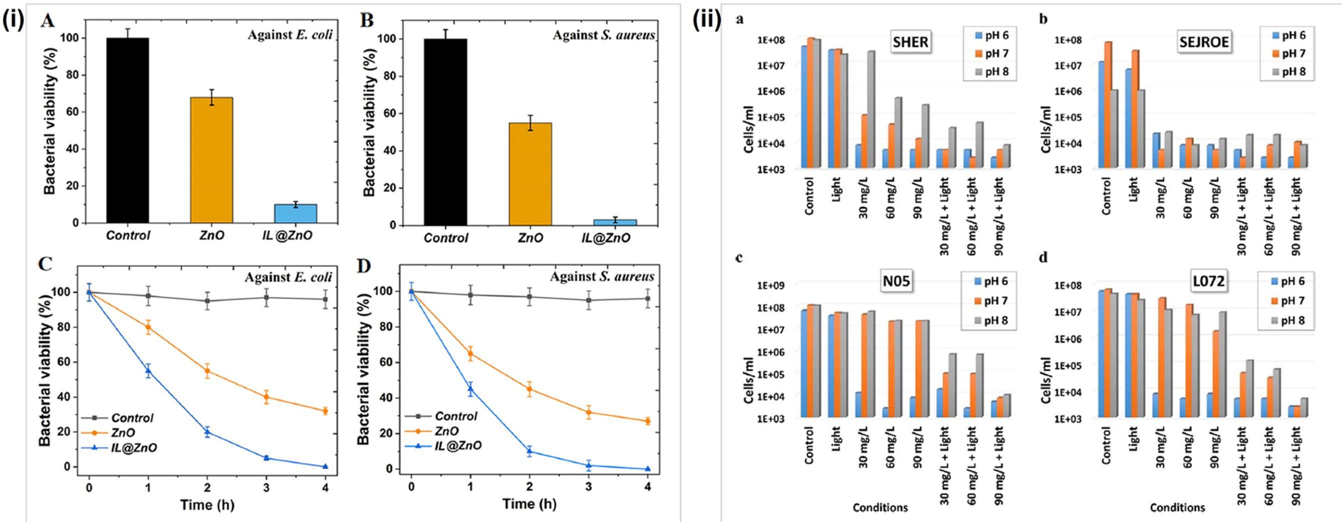

Figure 9. (i) Comparative viability studies of prepared materials against bacterial strains of (A) *E. coli* and (B) *S. aureus*. Growth curves over time of (C) *E. coli* and (D) *S. aureus* treated with ZnO and ionic liquid-functionalized ZnO nanosheets (IL@ZnO). Reproduced from ref 203. Copyright 2022 American Chemical Society. (ii) Comparison of *Leptospira* cell count from each treatment of sintered bulks ZnO with all four *Leptospira*: (a) SHER, (b) SEJROE, (c) N05, and (d) L072. Reproduced from ref 202. Copyright 2022 American Chemical Society.

4.1. Antibacterial Applications.

ZnO NSs show significant bactericidal potential against various Gram-positive and Gram-negative bacteria such as *E. coli*, *S. aureus*, *P. aeruginosa*, *Salmonella typhimurium*, *K. pneumoniae*,[188,201] and many others.[202−206] Some recent examples are listed in Figure 9.

Because of the presence of natural compounds, which should ensure a negligible cytotoxicity, ZnO NSs synthesized by biogenic methods are generally considered worthwhile for antibacterial applications. In this sense, several biological sources are involved in the preparation of biogenic ZnO NSs, and their bioactivity was tested as well. ZnO NSs from a native *B. cereus* strain were tested as antimicrobial agents showing a significant antibacterial activity at 50 μg mL^{-1} against *Burkholderia glumae* and *Burkholderia gladioli* with a significant zone of inhibition, and the cell numbers of the two pathogens in broth culture were reduced by 71.2% and 68.1%, respectively.[119] ZnO NSs biosynthesis was carried out using resin extraction from *Pistacia atlantica* as a reductant and capping agent, demonstrating a good antibacterial activity against *K. pneumonia*, *E. coli*, *S. aureus*, and *Proteus mirabilis*, with an inhibition zone of >20 mm by the agar well diffusion method.[207] Comparable results were reported by El-Moslamy and collegues, who proposed scalable setup for using endophytic *Streptomyces albus* strain to produce ZnO with higher synthesis yields (up to 345.32 g/L)[208] (Figure 10).

ZnO nanoflowers and nanoparticles ranging from 7 to 22 nm were produced from the leaf extracts of an ethnobotanical species, *Achyranthes aspera*, using two different zinc precursors (zinc acetate and zinc nitrate). The authors demonstrated a higher zone of inhibition (29 mm) of Gram-negative pathogen *E. coli* and Gram-positive pathogen *S. aureus*. In addition, MIC values of biogenic ZnO NSs were observed in the range of 40−60 μg/mL against *S. aureus*, *Lactobacillus acidophilus*, *Saccharomyces cerevisiae*, and *Candida albicans* as selected oral pathogens.[209] In this regard, several reviews and book chapters were published, offering an extensive overview of the plant-mediated synthesis of ZnO NSs and their antimicrobial potential.[79,152,157,210−217]

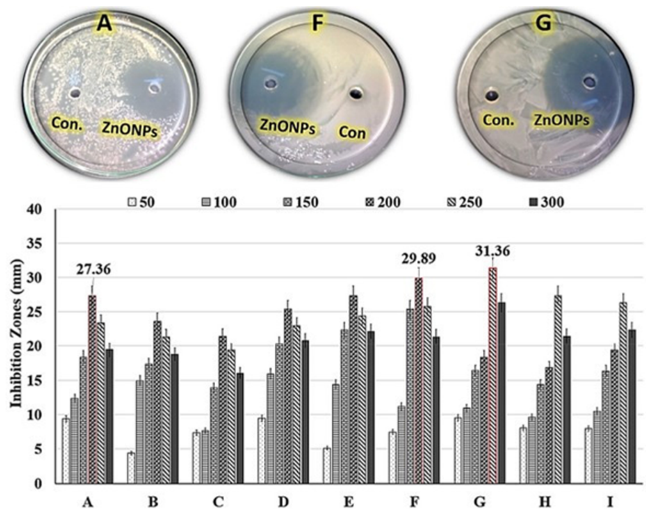

Figure 10. Antimicrobial activities of different doses of the controllable biosynthetic ZnO NPs (50, 100, 150, 200, 250, and 300 μg/mL) against some multidrug-resistant human pathogens, including (A) *E. coli*; (B) *K. pneumoniae*; (C) *P. aeruginosa*; (D) *S. aureus*; (E) *S. typhimurium*, (F) *S. pneumoniae*, (G) *C. albicans*, (H) *Candida krusei*; (I) *Candida tropicalis*. con = control: endophytic *S. albus* E56 cell-free mixed cell-free extract. From ref 208. CC BY 4.0.

One of the recent research trends involves coupling ZnO NSs with other materials in order to develop hybrid systems.[205] In this regard, low-density polyethylene films, commonly used in food packaging products, were modified with ZnO NSs to develop bioactive coatings, demonstrating a considerable inhibition (>90%) against *E. coli* and *S. aureus*.[218,219] In a similar way, cross-linked pectin-based films incorporating ZnO NSs were proposed, aiming to replace the typical polymers used in food packaging industry with more biocompatible and sustainable materials.[220] Because the common issue in the use of such biosourced polymers is the lack of tensile strength and other mechanical properties, it was proved that the addition of ZnO NSs to the cross-linked pectin films significantly improved their UV barrier and mechanical properties. In addition, the bionanocomposite coatings exhibited strong antibacterial activity against food-borne pathogenic bacteria. In particular, with 1.5% ZnO NSs, the antibacterial activities were 2.04 ± 0.04 and 2.11 ± 0.05 for *E. coli* and *S. aureus* in terms of log reduction of viable bacteria, respectively. This result indicated that the pectin-based films were effective according to the Z2801:2010 regulation, which requires a minimum antibacterial activity of 2.0.[220] This approach was involved in several works, proving the ZnO NS multifunctional ability to add synergistic features to the composites. For instance, chitosan-based films[221] and chicken skin gelatin/tapioca starch composite films[222] were modified by ZnO NSs, similarly proving both the improvement of physicochemical and mechanical properties of films and the efficacy of the bioactivity against food pathogens. In a similar way, poly(lactic-*co*-glycolic acid) (PLGA) is extensively applied as wound dressing and surgical suture in the biomedical field due to its excellent biocompatibility and biodegradation and low toxicity.[223] The creation of PLGA−ZnO NSs composites is of great interest, since the use of a PLGA matrix will control the release of ZnO NSs in the body, thereby providing controlled cytotoxicity and optimal antibacterial properties against specific bacterial strains.[224] Recently, ZnO NS-doped polytetrafluoroethylene (PTFE) coatings[225] have been proposed as eco-friendly multifunctional smartphone surface coatings with antireflectance, hydrophobic, and antibacterial properties, whereas an organosilicon composite based on borosiloxane and ZnO NSs has been developed as a dry disinfectant with reduced cytotoxicity.[226] ZnO NSs were widely used to modify textiles to confer them with bioactivity against pathogens. Among them, bioactive cotton-based fabrics[227−229] were modified by ZnO NSs in order to obtain bioactive materials. Tragacanth gum/ZnO nanoparticles (ZnO NPs) synthesized on the cotton fabric by ultrasound waves showed inhibition zones of 3.3 ± 0.1, 3.1 ± 0.1, and 3.0 ± 0.1 mm against *E. coli*, *S. aureus* and *C. albicans*.[228] Cotton khadi fabric modified with ZnO NPs demonstrated 95% to 99.9% reduction against *S. aureus* and *K. pneumoniae*[229] and UV protection. Cotton fabrics with in situ synthesized ZnO NPs exhibited inhibition zones of 15, 16, 13, and 14 mm against *Bacillus subtilis*, *S. aureus*, *E. coli*, and *P. auruginosa*.[230] The antibacterial activity of ZnO NPs-based materials turned out to be highly suitable for the development of biocompatible implants.[148,231,232] Recently, carbon-fiber-reinforced poly(ether ether ketone) (CFRPEEK) was proposed as an excellent candidate for orthopedic and dental implants. In order to inhibit implant-associated infections, ZnO NPs were distributed uniformly in the self-assembled polydopamine coating and stably immobilized on the CFRPEEK surface to achieve long-lasting antibacterial activity and reduce cytotoxic actions along with the efficient antimicrobial actions.[233] In vitro and in vivo studies on well-established bacteria isolated from orthopedic implant infections (*S. aureus* and *E. coli*) confirmed that hybrid PDA@ZnO NPs on the functionalized surface provided an effective antibacterial effect by means of three potential pathways: (a) ROS damage the intracellular contents, including proteins, DNA, ATP, etc., through intense oxidative stress reactions after being internalized into the bacterial cell membrane; (b) zinc ions released from the ZnO nanoparticles can cause mechanical damage to the bacterial cell wall, thus penetrating cell membranes to inhibit active transport and glucose metabolism and disrupt metal ion homeostasis and enzyme systems when the concentration reaches a specific level; (c) ZnO nanoparticles directly contact bacterial cell walls, causing damage to the membrane integrity and subsequent death.[233] Interestingly, ZnO NPs were coupled with antibiotics to exhibit synergistic efficacy and support the antibiotic resistance fight.[234−238] Finally, antibacterial ZnO NP-based materials were widely proposed for water purification, acting as both photocatalysts and antibacterial agents.[181,182,239,240]

Despite their recognized efficacy, examples of microbial resistance against metal and metal oxide NSs have been recently reported. However, it is still an unexplored field. In fact, only a limited number of studies have taken resistance development into account. Some NS resistance mechanisms include electrostatic repulsion, ion efflux pumps, expression of extracellular matrices, biofilms adaptation, and gene mutations.[241,242] One of the first comprehensive reviews on this topic was published in 2019.[241] For the specific case of metal oxide NSs (like ZnO ones), some bacteria (mostly Gram-positive ones) are able to regulate the electrical charge of their surface, which allows them to repel NSs with different charges,[242] becoming resistant. Additionally, the so-called "adaptive resistance" was identified for ZnO NSs: Zhang et al.[243] evaluated the effect of ZnO NSs on *E. coli*. These bacteria could develop resistance and grow at high ZnO concentrations (1 mg/mL); however, when the NSs were removed from the growth medium, the antibacterial sensitivity was fully restored.

4.2. Antifungal Applications. ZnO NPs have also been reported for their antifungal activities against many of the harmful yeasts and fungi. However, the sensitivity pattern of fungi to metal oxide NPs is very different from that of bacteria due to their distinct biological structures[244,245] (Figure 11).

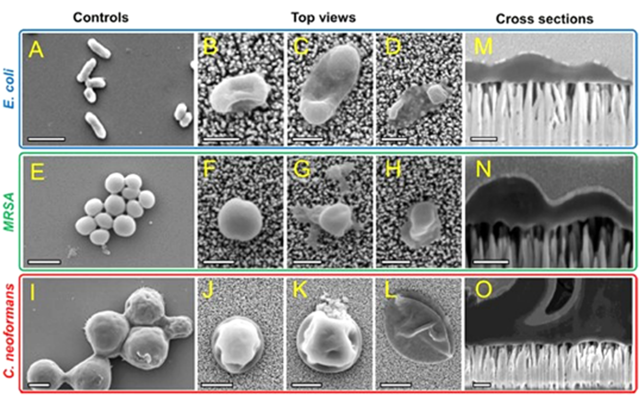

Figure 11. SEM characterization of the interaction between cells and ZnO nanowires. SEM images in top view (A−L) and cross section after FIB cutting (M−O) of cell interaction with control substrates (A, E, I) and ZnO NWs (all others). Scale bars for control samples are (A, I) 2 μm and (E) 1 μm. Scale bars for top views of ZnO NWs are (B−D, F−H) 500 nm and (J−L) 2 μm. Scale bars for cross sections are 200 nm. Reproduced from ref 245. Copyright 2021 American Chemical Society.

According to the review by Sun et al., the photon-induced generation of ROS and a poisoning effect due to Zn^{2+} release represent the two main contributions to the antifungal activity of ZnO NPs.[8] Specifically, the fungicidal mechanisms of ZnO NSs account for disrupting the cellular structure (e.g., cell wall or membrane and organelles), prohibiting biological macromolecular activity (e.g., protein, enzyme), preventing DNA replication, and disrupting the antioxidative system in a ROS-

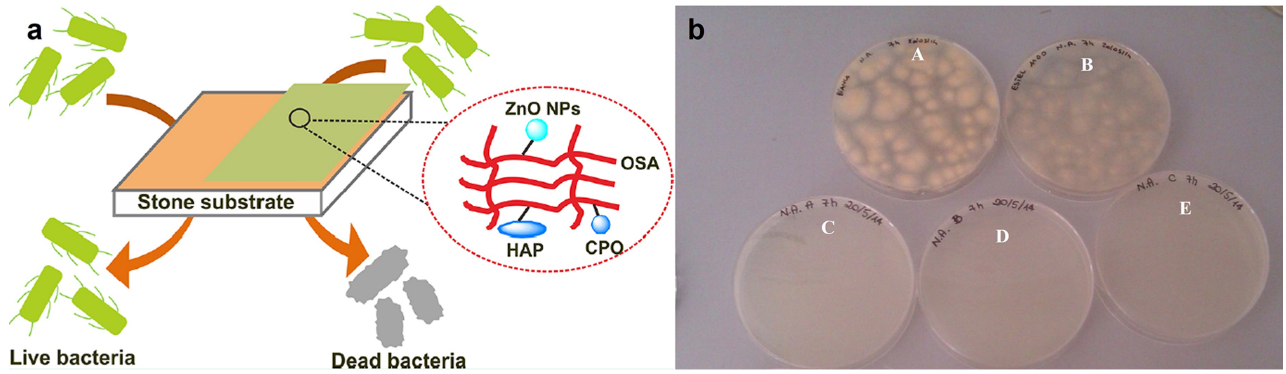

Figure 12. (a) Synergic combination of hydrophilic ZnO nanoparticles (ZnO NPs), calcium phosphate oligomers (CPO), and oxidized sodium alginate (OSA) as protective coatings on sandstone able to inhibit the growth of bacteria *E. coli* and *M. yunnanensis* and fungus *Aspergillus* sp. F6. Reproduced from ref 245. Copyright 2021 American Chemical Society. (b) *A. niger* colonies after 24 h of contact with ZnO-based nanocomposite-covered glass slides: (A) control plate; (B) Estel 1100; (C) Estel 1100/ZnO-NPs 0.15% w/w; (D) Estel 1100/ZnO-NPs 0.30% w/w; (E) Estel 1100/ZnO-NPs 0.60% w/w. Reproduced with permission from ref 122. Copyright 2015 Centre National de la Recherche Scientifique (CNRS) and Royal Society of Chemistry.

Table 3. Overview of the Main Antiviral Applications of ZnO-Based Nanomaterials

ZnO NSs synthesis method	size(s) and shape(s)	tested virus(es)	composite or functionalization	ref
Mentha spicata leaf extract	10−80 nm, spherical	tobacco mosaic virus (TMV)	–	250
solvothermal	200 nm, spherical	H1N1, HCoV-229E	triptycene organic molecules	251
flame transport synthesis	400−600 nm, tetrapods	genital herpes simplex virus II (HSV-II)	poly(vinyl butyral)	252
Pelargonium zonale leaf extract	∼ 5 nm, spherical	HCoV-229E	–	253
Cestrum dinurum leaf extract	3−5 nm, spherical and hexagonal	severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	–	254
orange peel oil extract	20−30 nm, spherical	SARS-CoV-2	hesperidin-capped	255
sol−gel	∼ 20 nm, spherical	TMV	–	256
commercial powders	20−50 nm, spherical	H1N1	PEG-capped	257
sol−gel	∼20 nm, spherical, ∼900 nm tetrapods	hepatitis C (HCV) and hepatitis E (HEV) viruses	–	258
solvothermal	20−30 nm, spherical	human cytomegalovirus	chitosan/benzyloxybenzaldehyde	259
Stoechospermum marginatum seaweed extract	80−120 nm, spherical	dengue fever virus	fucoidan-capped	260
electrochemical synthesis	∼ 20 nm, spherical; 300−500 nm, wire-like	SARS-CoV-2	poly(ethylene oxide)	124
commercial powders	∼ 200 nm, spherical	SARS-CoV-2	cellulose acetate for synthetic fibers	261
Plumbago indica leaf extract	∼ 30 nm, spherical and hexagonal	HSV-1	–	262
flame transport synthesis	100−200 nm, snowflake- and urchin-like	HSV-1	–	263

and/or Zn^{2+}-mediated manner, which are very similar to the antibacterial mechanisms. In this context, Alhazmi and colleagues proved that 25 nm ZnO NPs synthesized by precipitation method showed an impactful antifungal effect against isolates of azole-resistant *Aspergillus flavus*.[246] Xerogel formed of Ag NPs and ZnO NPs exhibited satisfactory susceptibility against *Trichophyton mentagrophytes* and *Trichophyton verrucosum*, dermatophyte fungi that often cause a superficial skin disease called dermatophytosis.[247] ZnO NP−lignin aggregates showed significant antifungal activity against selected fungal strains like *Aspergillus fumigatus*, *Aspergillus penicilloides*, *C. albicans*, *Conidiobolus coronatus*, and *Microsporum cookei*.[248] The 40 nm ZnO NPs synthesized by a conventional chemical procedure demonstrated antifungal action on strains of *Aspergillus niger* and *Botrytis cinerea*, being more efficient in inactivating *B. cinerea*.[31] ZnO-based material also found application as antifungal coating for stone artworks in cultural heritage field (Figure 12).[122,123,245]

4.3. Antiviral Applications. ZnO NSs have been reported to exhibit considerable antiviral activity against a variety of viruses. The mechanism of action lying beyond the antiviral strength of ZnO is the stimulation of the so-called adaptive immune response through toll-like receptor signaling pathways and protein downstreaming. This mechanism results in the secretion of proinflammatory cytokines which can inhibit viral proliferation.[249] A nonexhaustive summary of the more recent antiviral applications of ZnO NSs is reported in Table 3.

It is noteworthy that most of the papers available in literature deal with the use of Zn^{2+} ions as antiviral agents, rather than ZnO NSs, possibly in combination with other molecules like lactoferrin, heparin, etc.[264−274] Zinc ions can penetrate cell walls (especially when driven by ionophores), augmenting the intracellular Zn^{2+} concentration and subsequently impairing virus replication.[275] Bhatti and DeLong[276] recently reviewed the antiviral application of different nanomaterials, including ZnO NSs: in that paper, ROS generated

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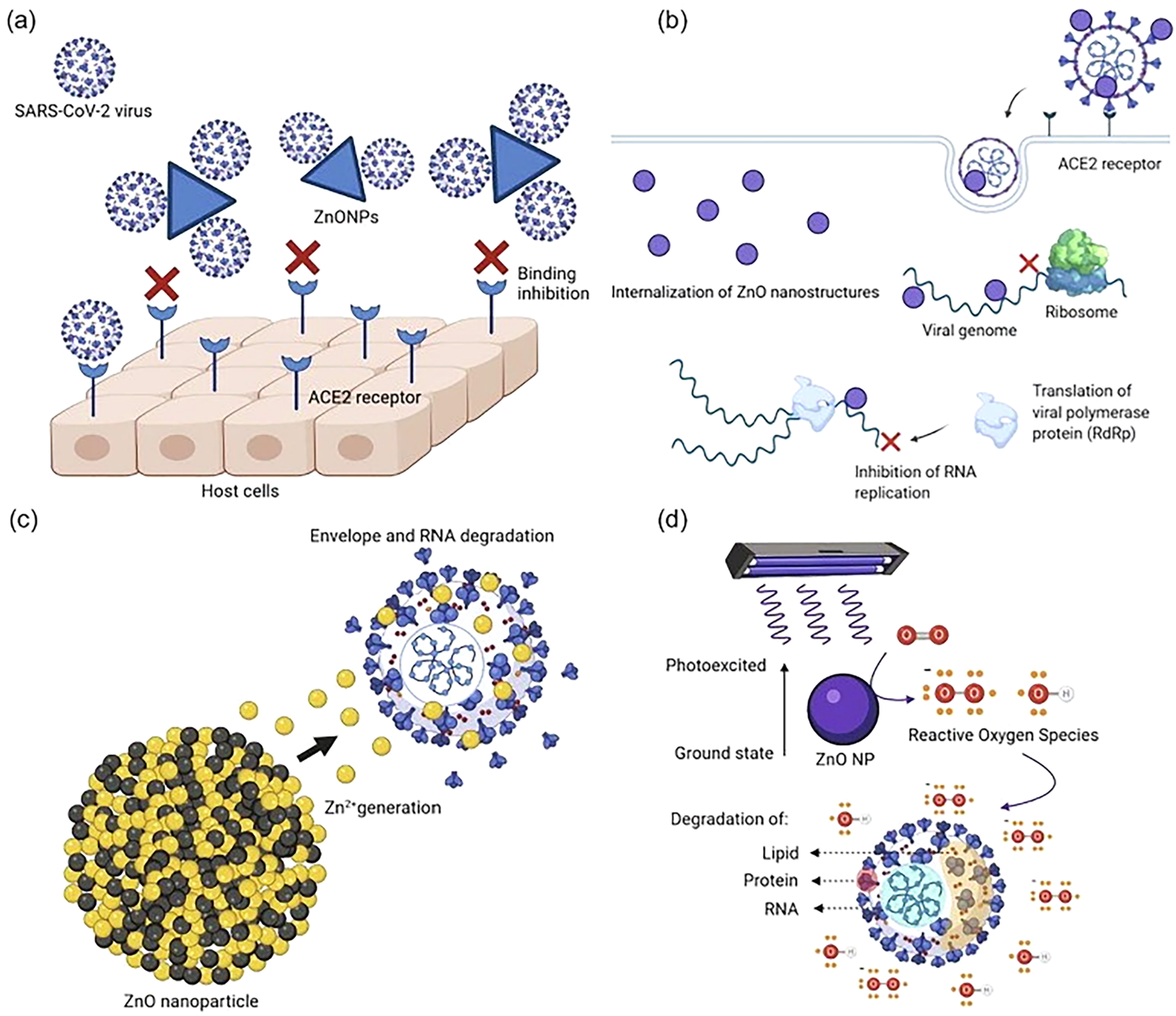

Figure 13. Possible mechanisms of antiviral activity of ZnO against SARS-CoV-2. (a) Design of ZnO nanostructures for the possible anchoring of SARS-CoV-2 virions, thus inhibiting interactions with host cell receptors. (b) Internalization of ZnO nanostructures for the inhibition of early stages of the viral replication cycle. (c) Ion release as a surface attack mechanism to disrupt the plasmid and RNA virus integrity. (d) Photocatalytic generation of reactive oxygen species for the possible degradation of the lipid, protein, and nucleic structure of SARS-CoV-2. From ref 283.

through photocatalytic reactions driven by UV−Vis light on ZnO NSs are indicated as the main species responsible for damaging of the viral envelopes, interfering with viral entry and replication.[249]

Indeed, before the COVID-19 pandemic, the use of ZnO NSs as antiviral agents was not as massively diffused as that of their antimicrobial applications. Due to the inability of many viruses to spread outside the body (e.g., HIV, HCV, etc.),[277] antiviral applications other than medicinal and biomedical ones have attracted little attention in the past. However, SARS-CoV-2 can remain viable on surfaces for days.[278] Human-to-human transmission of SARS-CoV-2 has been extensively described; besides droplet contagion, touching of contaminated surfaces also rapidly became a serious issue in 2020. In this panorama, some disinfectant agents could effectively reduce coronavirus infectivity within 1 min: 62−71% ethanol, 0.5% hydrogen peroxide, or 0.1% sodium hypochlorite.[279] Other mixtures, such as 0.05−0.2% benzalkonium chloride or 0.02% chlorhexidine gluconate proved to be less effective.[280] An efficient surface disinfection helped dramatically in ensuring early containment and prevention of surface-driven infections: ZnO NSs were revealed to be powerful collaborators in this framework. In fact, as anticipated before, Zn^{2+} ions are known to exhibit anti-SARS-CoV-2 properties. These ions can inactivate virus adsorption/entry in the host cell, catalyze the production of ROS, hinder viral replication, and bind some specific viral proteins.[281] As an example, Zn^{2+} ions inhibit two essential proteins for the CoV lifecycle: the RNA-dependent RNA polymerase (RdRp) and the 3C-like proteinase (3CL), which are both involved in viral replication.[282] The action of ZnO NSs against SARS-CoV-2 was recently reviewed,[283] and their possible interaction mechanisms were presented (Figure 13). COVID-19 outbreak dramatically increased the use of nanomaterial-based antivirals (ZnO NSs being among the most used); Jamshidinia et al.[284] reviewed this topic, with peculiar attention on toxicity on health and environmental concerns of used NSs.

We have recently investigated ZnO antiviral properties for the preparation of human-safe and effective surface coatings against COVID-19.[124] Poly(ethylene oxide) embedding electrosynthesized ZnO NSs showed good activity toward SARS-CoV-2, the persistence of the virus being significantly

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lowered on common-touch surfaces modified by the active coating. We also correlated the effectiveness of the composite coatings with the entity of ionic release. The maximum concentration of Zn^{2+} reached in this study is lower than the no observed adverse effect level (NOAEL) safety limit reported by the EU.[285]

Other mechanisms of action were postulated for different viral families. An interesting overview on the antiviral application of tetrapod-shaped ZnO NSs was published in 2021, about herpes viruses (HVs).[286] The main issue related to these viruses is that they are among the ubiquitous human infections and persist for a lifetime as a latent infection in host cells. The latency can reactivate due to specific external conditions, thus causing a multitude of severe symptoms.[287] Common antiviral drugs are not always effective in the treatment of HV-caused infections. The infection relies on multivalent interactions between virions and cells; however, most of the antiviral drugs are monovalent inhibitors, which cannot efficiently block a multivalent process.[288] ZnO NSs with tetrapod symmetry can efficiently stop HV at multiple steps of infection and provide preventive and therapeutic benefits.[289]

Based on the previous discussion, what is the advantage of using ZnO NSs instead of Zn^{2+} ions? The main benefit of using NSs resides in the controlled and long-lasting release of antiviral Zn^{2+} ions from ZnO NSs. This controlled release ensures, in general, the reduction of surface-driven infections and the availability of virological-safe biomedical equipment.[283]

5. CONCLUSION: OPEN ISSUES AND CHALLENGES

Are ZnO NSs safe? In the last years, this question has been raised especially in consideration of their direct use in health and food sectors as well as for their possible direct release and fate in the environment. In a recent review[290] it has been clarified how cytotoxic effects depend strongly on surface charge and size of NSs. Typically, positively charged small NPs are more subjected to cell internalization. However, other aspects should be considered to evaluate toxicity, including NP aggregation in biological fluids, dissolution kinetics, sedimentation phenomena which are dependent on physicochemical properties of contacting media, and types of NSs. In particular, the role of Zn^{2+} ions in combination with ZnO NSs needs to be addressed separately.[291]

As with all metal and metal oxide NSs, the widespread use of ZnO NSs leads to both benefits related to their use and to potential risks for humans and the environment. The massive use of this nanomaterial in real-life products can pose a threat at both the consumer and professional levels. The widespread use of ZnO NSs can have short-term and long-term effects on human health and can cause damage to cultivations of sensitive plant varieties.[6,292] ZnO NSs can exert their cytotoxicity through inhalation, dermal, and oral routes, although their tolerability is quite high.[6] It seems that the dissolved Zn^{2+} ions play a main role in toxic effects of ZnO NSs.[293] Such cytotoxicity has been exerted also toward cancer cells: the ability of ZnO NSs to selectively trigger the formation of ROS and induce apoptosis has been recently outlined in many reviews.[143,294,295] ZnO NSs showed specific toxicity in cancer cells, generating ROS and destructing mitochondrial membranes. ZnO NSs can also be used as effective carriers for targeted chemotherapeutic delivery and cancer cell detection.[296] However, much work is still needed to clarify the potential cytotoxicity of NSs and their correct use under proper conditions.

As mentioned, the fate of nanomaterials in waters[297] or other media can be critical, being particularly harmful also in combination with additional pollutants such as microplastics.[298]

The preparation of ZnO NS formulations with known and controlled size, surface charge, and shell composition should be regarded as the Holy Grail for proper evaluation of cytotoxic and adverse effects. However, in this scenario, the direct use of ultrasmall nanoparticles for antimicrobial applications is highly recommended. The irreversible immobilization of ZnO NSs in protective/embedding coatings should be preferred, thus preventing the direct NS release in biofluids/environment.

Moreover, the discovery or development of new antimicrobial molecular drugs is unable to catch up to the emerging AMR problem. NSs have been proven to be effective against antibiotic-resistant bacteria. However, the nanoresistance issue could become a burden if NS-containing real-life products are used without specific regulations, and the fate of these NSs is uncontrolled and unknown. Therefore, we support the idea that additional mechanistic studies about the antimicrobial activity and cytotoxicity of ZnO NSs should be performed by using standardized protocols for reliable and reproducible results. In this way, it will be possible to build more efficacious and safe ZnO NSs, less prone to AMR, just by proper tuning of the synthesized nanomaterial. This holds true also thanks to the development of synergistic nanoantimicrobials, i.e., NSs coupled/coated with molecular antimicrobial agents. In such systems, the presence of multiple antimicrobial moieties makes resistance development much more difficult: in principle, an infinite number of NS−molecular agents are possible.

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Author Contributions

[§]M.I. and M.C.S. contributed equally to the work. M.I. drafted the paragraphs on hydro/solvothermal syntheses and antibacterial and antifungal applications, collected literature for tables, and prepared the figures. M.C.S. drafted the paragraphs on biogenic syntheses and antiviral applications of ZnO NSs. L.T. contributed to the section on electrochemical processes and revised the final version of the manuscript. R.A.P. wrote the section on sol−gel and electrochemical approaches and the final section on open issues and challenges, conceived the structure of the review, and revised the final version of the manuscript. N.C. supervised the activities and edited the manuscript.

Notes

The authors declare no competing financial interest.

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