Advances in antibacterial activity of zinc oxide nanoparticles against *Staphylococcus aureus* (Review)

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Abstract. Nanoparticles (NPs) are one of the promising strategies to deal with bacterial infections. As the main subset of NPs, metal and metal oxide NPs show destructive power against bacteria by releasing metal ions, direct contact of cell membranes and antibiotic delivery. Recently, a number of researchers have focused on the antibacterial activity of zinc oxide nanoparticles (ZnO NPs) against *Staphylococcus aureus* (*S. aureus*). Currently, there is a lack of a comprehensive review on ZnO NPs against *S. aureus*. Therefore, in this review, the antibacterial activity against *S. aureus* of ZnO NPs made by various synthetic methods was summarized, particularly the green synthetic ZnO NPs. The synergistic antibacterial effect against *S. aureus* of ZnO NPs with antibiotics was also summarized. Furthermore, the present review also emphasized the enhanced activities against *S. aureus* of ZnO nanocomposites, nano-hybrids and functional ZnO NPs.

Contents

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1. Introduction

Staphylococcus aureus (*S. aureus*) is a gram-positive pathogen that can lead to numerous infectious diseases, such as pneumonia, endocarditis, osteomyelitis, skin and soft tissue infections, bacteremia and sepsis (1). At the same time, the threat caused by *S. aureus* infections has increased significantly in humans as well as in animals (2,3). In clinical practices, antibiotics are effective way to treat *S. aureus* infections. With the use of antibiotics (especially overuse or misuse of antibiotics), antibiotic resistant *S. aureus* strains, such as methicillin-resistant *S. aureus* (MRSA), have spread both in hospitals and communities and also persist in the home environment, which poses a great threat to human health (4,5). It is estimated that 700,000 persons succumb to antibiotic-resistance bacteria including MRSA and this number is predicted to grow to 10 million by 2050 (3). In order to deal with this, increasing efforts have been made to discover new therapeutic strategies to fight against *S. aureus* infections, such as bacteriophage (6,7), vaccines (8-10), monoclonal antibodies (11,12), recombinant endolysins (13), anti-persistent bacteria therapies (14), antibacterial peptide (15,16), natural plant components (17-19) and nanoparticles (NPs) (20,21).

NPs, being <100 nm, are one of the novel promising methods to deal with bacterial infections, including *S. aureus* infections (22,23). The antibacterial activity of NPs is mostly attributed to their special characteristics, such as well-distributed size, perfect spherical shape, positive surface charge and hydrophobicity (24,25). NPs begin their antibacterial effects by the direct interplay with cell surface, involving the destruction of cell wall peptidoglycan and membrane protein and interference in energy metabolism (ATPase inhibition and electron transport disruption). Then, NPs can penetrate into cytoplasm and cause great damage to intracellular components, including nucleic acids, proteins, lysosomes and ribosomes (26). Additionally, oxidative stress induced by excess releasing of reactive oxygen species (ROS) also plays a substantial role in inducing lipid peroxidation on the bacterial cell membrane (27). As well as the aforementioned mechanism, metal NPs have specific ways to resist pathogenic microorganisms by releasing metal ions and producing different ROS (28). Several metal (gold, silver, copper and zinc) NPs

and their metal oxide NPs have been reported to have distinctive antimicrobial properties against *S. aureus* (29,30) and they were also shown to be the carriers that can deliver antibiotics to target sites (22,31). Fig. 1 shows the properties, antibacterial mechanism against *S. aureus* and antibiotics delivery ability of zinc oxide nanoparticles (ZnO NPs).

There are a number of studies reporting the antibacterial property of ZnO NPs against *S. aureus* (32-34). ZnO NPs reduce the biofilm of *S. aureus* by inhibiting biofilm genes expression, such as *ica A*, *ica D* and *fnb A* (35). In Kahandal *et al* (36), the biofilm formation of *S. aureus* was inhibited markedly by 95.39 % when treated with 125 μg/ml of ZnO NPs for 5 h. Abdelraheem *et al* (37) observed that ZnO NPs presented antibacterial activity against multidrug resistant *S. aureus*, such as methicillin, vancomycin and linezolid resistant *S. aureus*. Irfan *et al* (38) confirmed the antibacterial activity of ZnO NPs against *S. aureus* and MRSA with the zone of inhibition (ZOI) of 21±2 and 17±2 mm, respectively. El-Masry *et al* (39) also reported that ZnO NPs (20 nm and concentration of 20 mM) inhibited 10^5 and 10^7 CFU/ml *S. aureus* with ZOI of 26 and 22 mm, respectively. Currently, there is a lack of a comprehensive review on ZnO NPs against *S. aureus*. Therefore, the present study reviewed the antibacterial activity against *S. aureus* of ZnO NPs fabricated by various synthetic ways, especially the green synthetic ZnO NPs. It also summarized the synergistic antibacterial effects against *S. aureus* of ZnO NPs in combination with antibiotics. Furthermore, it highlighted the enhanced activities against *S. aureus* of ZnO nanocomposites, nano-hybrids and functional ZnO NPs.

2. Chemically and physically synthesized ZnO NPs against *S. aureus*

Commonly, ZnO NPs can be synthesized by using top-down and bottom-up methods that include diverse physical and chemical ways (40) (Fig. 2). Top-down approaches cut massive materials into NPs physically, including ball milling, ion sputtering, laser ablation, metal etching and pyrolysis. According to Massoudi *et al* (41) research, ZnO NPs made by high-speed ball milling inhibit *S. aureus* with the largest ZOI of ~13.5±0.5 mm. It was also found that ZnO NPs synthesized by microwave heating displayed the ZOI of ~16 mm against *S. aureus* (42). Bottom-up ways fabricated atoms and molecules into nano-sized particles, which included chemical reduction, sol-gel method, chemical vapor deposition, molecular condensation and even green synthesis (43). Different synthesis processes bring about various physicochemical properties of metal NPs such as size, shape, dispersity and stabilization diversity, which determine the antibacterial efficiency (44,45). Table I shows the characteristics and anti-*S. aureus* capacity of ZnO NPs made by several methods. In Bai *et al* (46), small molecule ligand solvothermal synthesized ZnO NPs showed size-related antibacterial effect and the minimum inhibitory concentration (MIC) of 4 nm ZnO NPs against *S. aureus* was 6.25 μg/ml, which is lower than the MIC of 10 nm ZnO NPs at ~25 μg/ml. In an antimicrobial test of solution-polymerization-method synthesized ZnO NPs, it was discovered that *S. aureus* was more susceptible to nanoparticle size than *E. coli* (47). The co-precipitation method is also frequently used to synthesize ZnO NPs that show the lowest MIC against *S. aureus* compared with other bacteria (48). Moreover, by using an easy chemical method, diethylene-glycol-mediated ZnO NPs were made and they had antibacterial activity against *S. aureus* with the ZOI of 14 mm and showed the excellent *S. aureus* biofilm control (49). It was also reported that *S. aureus* cell leakage was observed after exposure to mechano-chemical synthesized ZnO NPs (50). Although a great number of physicochemical synthetic methods have been found to make ZnO NPs for *S. aureus* treatment, some demerits such as high cost, toxicity and instability still place restrictions on their large-scale antibacterial applications (43).

3. Green-synthesized ZnO NPs against *S. aureus*

Recently, green biological materials drew much attention to researchers for their environment-friendly, cost-effective, low-toxicity and useful properties to make ZnO NPs (26). There are a number of types of biological materials such as bacteria, fungi, algae and plant extracts (51,52) (Fig. 3), which serve as reducing agents, capping agents, stabilizers and ligands during the synthesis of ZnO NPs (26) and their effects are ion reduction, size and shape control, NPs surface stabilization, metal passivation and coating, respectively, which are important to the antimicrobial properties of ZnO NPs (26,53). The antibacterial properties of green-synthesized ZnO NPs against *S. aureus* are in Table II.

Plant extracts synthesis. Due to different synthetic raw materials, plant-derived ZnO NPs are provided with multifarious characteristics. Triangle-like M-ZnO-NPs and B-ZnO-NPs were made by *Mentha spicata* and *Ocimum basilicum* acting as capping, stabilizing and reducing agents with size of 24.5 and 26.7 nm, respectively. These types of ZnO NPs had antibacterial properties against *S. aureus* (ATCC 25923) with a 14.73 mm ZOI with 0.01 g/ml M-ZnO-NPs (54). In Sachin *et al* (55), ZnO NPs synthesized by using *lychee* peel extract were spherical and small (<10 nm) and were also proved to combat *S. aureus* (ATCC25923) with 15 mm ZOI of 100 μg/ml ZnO NPs. In Mohammed *et al* (56), zinc nitrate hexahydrate and *Cymbopogon citratus* extracts were used to synthesize ZnO NPs, which killed *S. aureus* cells with a MIC of 88.13±0.35 μg/ml. In Mushtaq *et al* (57), methanol and water leaf extracts of *Viscum album* were applied to fabricate ZnO NPs that were quasi-spherical with size of 13.5 nm and which showed considerable inhibitory effects against *S. aureus* with a ZOI of 39±0.3 and 40±0.3 mm, respectively. Due to having a higher content of DNA gyrase-B inhibitor, the water extracts of ZnO NPs were proved to be more effective in limiting bacterial growth. ZnO NPs with flower-shaped structures were created by a green nanotechnology facility in Hasan *et al* (58) and showed 90.9% inhibition against *S. aureus*. It is noteworthy that the ZnO NPs showed more durable antimicrobial activity than Ag NPs in *in vivo* tests, which may be attributed to their distinctive morphology and massive active surface sites. In Irfan *et al* (59), green-synthesized ZnO NPs by Gum *Acacia modesta* expressed antimicrobial ability against MRSA with a ZOI of 16±2 mm. Alallam *et al* (60) also observed that ZnO NPs made by pure curcumin had a great ability to combat MRSA. Notably, these green-synthesized ZnO NPs showed a minimal cytotoxicity compared with

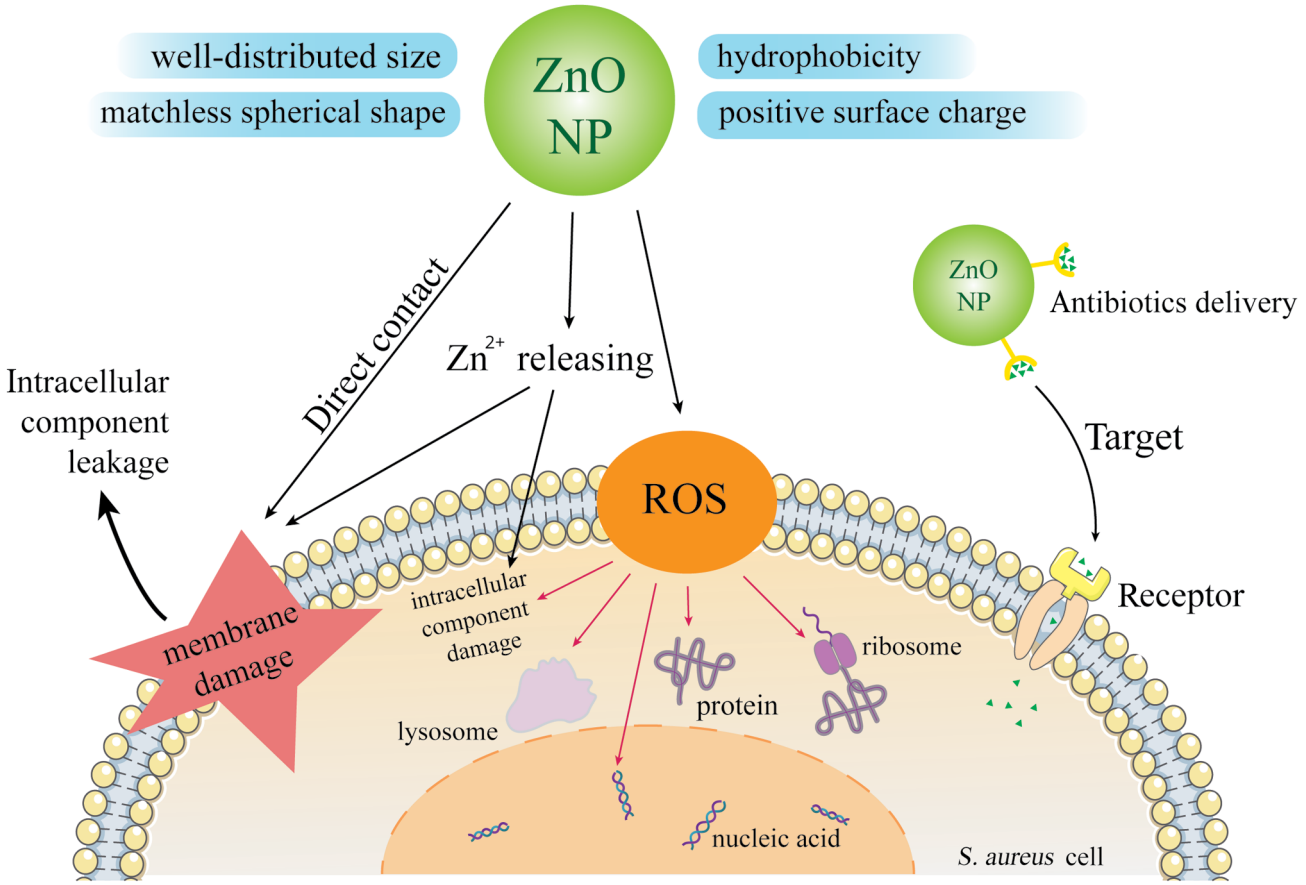

Figure 1. The excellent properties, antibacterial mechanism against *S. aureus* and antibiotics delivery ability of ZnO NPs. ZnO NPs, zinc oxide nanoparticles; *S. aureus*, *Staphylococcus aureus*; ROS. reactive oxygen species.

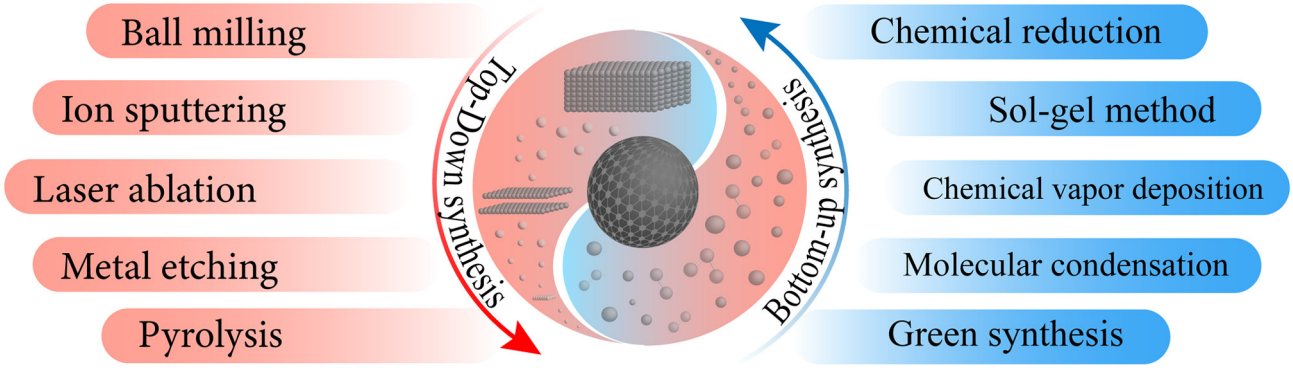

Figure 2. Top-down and bottom-up synthesis methods of ZnO NPs. ZnO NPs, zinc oxide nanoparticles.

chemically synthesized ZnO NPs (61). Furthermore, in Ting *et al* (53), ZnO NPs biosynthesized by using the aqueous extract of *Andrographis paniculata* leaves demonstrated a high inhibition on *S. aureus* and then controlled periimplantitis. ZnO NPs synthesized by using ethanolic extracts of *Eupatorium odoratum* are reported to show more than 97% biofilm inhibition of *S. aureus* that could be applied to reduce central venous catheter associated infections (61).

Algae synthesis. Algae are known as 'bio-nano-factories' due to their various properties, such as low risk of environmental toxicity, simple processing methods and the ability to redox metals (62). In addition, algal extracts are full of bioactive molecules that can be used as reducing and stabilizing agents. The biosynthesis of ZnO NPs using microalgae was authenticated to be a cost-effective method and the ZAA2 strain microalgae-synthesized ZnO NPs showed outstanding antibacterial activity with the largest ZOI of ~20 mm against *S. aureus* (63). In addition, by using *Chlorella vulgaris* as green resource, biogenic ZnO NPs were produced having significant antibacterial activity against MRSA, attributed to their excellent size distribution and surface energy (64). Researchers have also investigated the phyco-synthesis of UFD-ZnO NPs using extract of *Ulva fasciata* Delile. The destructive power

Table I. The characteristics and anti-*S. aureus* activity of top-down and bottom-up synthesized ZnO NPs.

First author/s, year	Method type	Method	Size	Shape	Bacterial strain	MIC	ZOI	(Refs.)
Massoudi *et al*, 2022	Top-down synthesis	Ball milling	148±68 nm	Hexagonal	*S. aureus*		13.5±0.5 mm	(41)
Yusof *et al*, 2019		Microwave heating	50-130 nm	~Spherical	*S. aureus*		16 mm	(42)
Bai *et al*, 2015b		Solvothermal synthesis	4 nm, 10 nm	Wurtzite structure	*S. aureus* (ATCC 6538)	6.25 and 25 µg/ml		(46)
Manzoor *et al*, 2016		Mechano-chemical milling	<20 nm	Spherical	MRSA	0.625 mg/ml		(50)
El-Gendy *et al*, 2022		Laser-ablation	9.8 nm	Spherical	*S. aureus* (ATCC 43300)			(126)
Navarro-López *et al*, 2021 structure	Bottom-up synthesis	Solution-polymerization method	<20 nm	Hexagonal wurtzite	*S. aureus* (ATCC 33594)	1 mg/ml		(47)
Manyasree *et al*, 2018		Co-precipitation	35 nm	Spherical	*S. aureus* (MCC-2408)	4 mg/ml	24±0.35 mm	(48)
Sajjad *et al*, 2021		Co-precipitation	17.11-22.56 nm	Spherical to hexagonal disks and rodlike	MRSA		23 mm	(139)
Al-Mosawi *et al*, 2023		Wet chemical precipitation method	18.47-25.19 nm	Spherical	MRSA	25-50 µg/ml	17.62±2.65 mm	(140)
Kim *et al*, 2020		Solvothermal synthesis	50 nm	Spherical	*S. aureus*		4 mm	(141)
Hozyen *et al*, 2019		Sonochemical method	41 nm	Hexagonal	*S. aureus*	20 mg/ml		(142)
Mahamuni *et al*, 2018		Polyol synthesis	15-100 nm	Oval to rod	*S. aureus* (NCIM 2654)	10-20 µg/ml	14 mm	(49)
Khan *et al*, 2014		Sol-gel method	23.7-88.8 nm	Flower-shaped	*S. aureus*	0.5 mg/ml	23 mm	(143)
Dadi *et al*, 2019b		Sol-gel method	3 nm	Spherical	*S. aureus* (ATCC 6538)		32 mm	(32)
Gharpure *et al*, 2021		Co-precipitation	60-250 nm	Rod, pear and almond-shaped	*S. aureus* (PTCC1112) and *S. aureus* (ATCC6538p)	2.5 µg/ml		(144)
Wahab *et al*, 2010		Non-hydrolytic solution process	20-30 nm	Spherical	*S. aureus*	15 µg/ml		(145)

ZnO NPs, zinc oxide nanoparticles; *S. aureus*, *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MIC, minimum inhibitory concentration; ZOI, zone of inhibition.

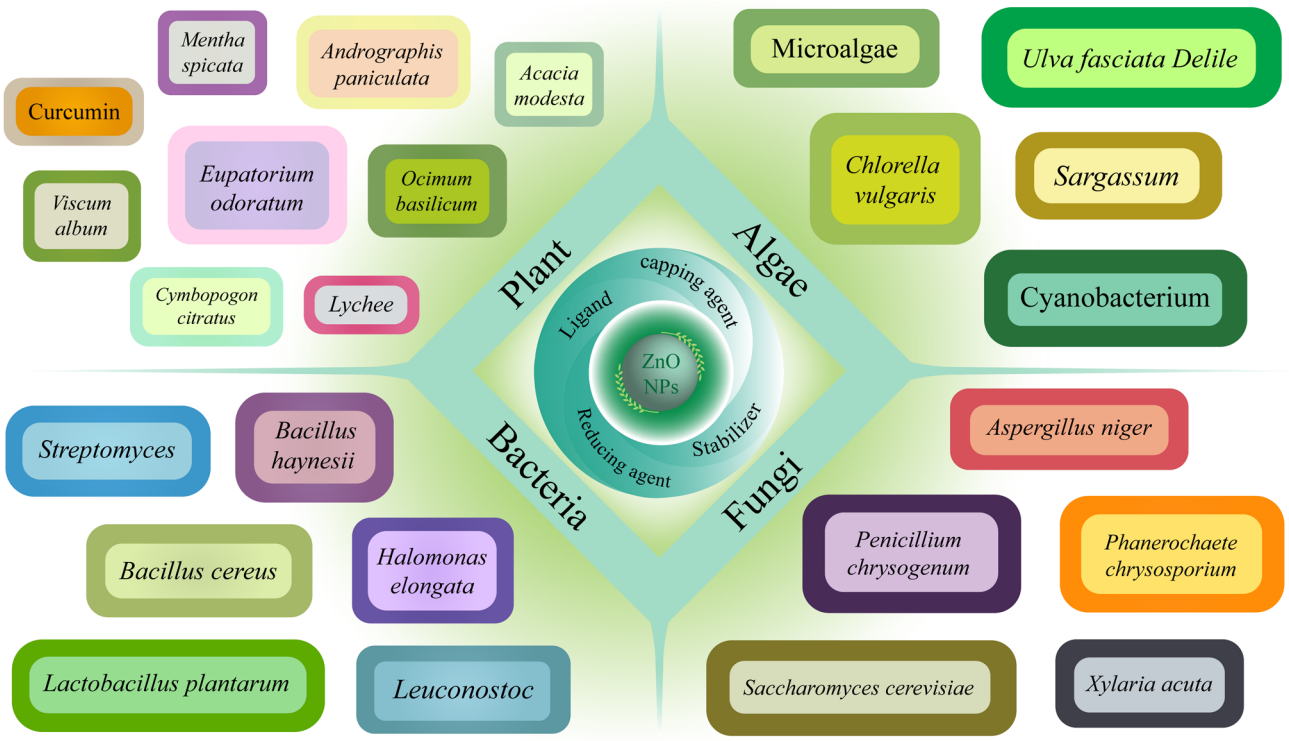

Figure 3. Raw materials classifications and functions of green synthesis for ZnO NPs. ZnO NPs, zinc oxide nanoparticles.

of UFD-ZnO NPs against *S. aureus* (ATCC 25923) was time-dependent, while the MIC and ZOI were recorded at ~17.5 μg/ml and 24.9±1.5 mm, respectively (65). In a recent study, *Sargassum* extracts have been used to synthesize ZnO NPs and the ultrasound-assisted green synthesized ZnO NPs showed the highest inhibition against *S. aureus* by 99% compared with ZnO NPs alone (66). As one of the phototrophic bacteria, cyanobacteria are the source of bioactive compounds as well as the raw material of ZnO NPs synthesis. By using cell extract of a new cyanobacterial strain *Desertifilum* sp. EAZ03, ZnO NPs have been made that possess considerable antibiofilm and antimicrobial effects against *S. aureus* (ATCC 59223) with an MIC value of 32 μg/ml and the minimum bactericidal concentration value of 64 μg/ml (67). Similarly, Ebadi *et al* (68) synthesized ZnO NPs using the cell extract of the cyanobacterium *Nostoc* sp. EA03, which were also discovered to destroy *S. aureus* biofilms and had low cytotoxicity on lung fibroblast cells.

Bacterial synthesis. With their lower purification cost and higher productivity compared with other microorganisms, bacteria are also considered as the raw materials to create ZnO NPs (69,70). According to a biosynthesis test of Yusof *et al* (71), *Lactobacillus plantarum TA4*, a microorganism isolated from fermented food, was proved to synthesize ZnO NPs with concentration- and shape-dependent antibacterial capacity. In addition, cell-free supernatant (CFS) and cell-biomass (CB) taken from *L. plantarum* TA4 were used as reducing agents to synthesize ZnO NPs, respectively. Although the MIC value to inhibit *S. aureus* of ZnO NPs-CB was lower compared with ZnO NPs-CFS, ZnO NPs were more conveniently purified by CFS (71). From this, it is indispensable to weigh up the pros and cons of different synthetic materials in order to choose the optimal raw material under different demands and experimental environments. In Rehman *et al* (72), *Bacillus haynesii* isolated from date palm plant was employed as the reducing agent to establish an eco-friendly nanobiofactory. ZnO NPs mediated by *Bacillus cereus* showed a spherical shape with median size of 50±5 nm, which damaged *S. aureus* cell surface by direct contact (72). *Streptomyces* purified from waste soil can be used to biosynthesize ZnO NPs and the antibacterial effects were identified to combat multiple isolates of *S. aureus* (73). Taran *et al* (74) explored the optimum condition to biosynthesize ZnO NPs by using *Halomonas elongata* IBRC-M 10214 through the Taguchi method (75). Results showed that these ZnO NPs were stable, pure and nontoxic, able to fight against multi-drug resistant bacteria such as *S. aureus* ATCC 43300. Strain C2 isolated from the genus *Leuconostoc* of lactic acid bacteria has been employed to biosynthesize metal NPs, including ZnO NPs and Au NPs. According to Kang *et al* (76), the C2-ZnO NPs expressed a lower MIC value of 512 μg/ml compared with C2-Au NPs (MIC: 1024 μg/ml) against *S. aureus*.

Fungal synthesis. A number of studies have reported that fungi can be used for synthesizing ZnO NPs. Sharma *et al* (77) used *Phanerochaete chrysosporium* to make ZnO NPs with advantages in terms of stability, simple processing, antimicrobial activity and non-cytotoxicity. Mohamed *et al* (78) produced fungal-synthesized ZnO NPs of 9-35 nm by using *Penicillium chrysogenum* and found that the ZnO NPs had antibacterial and antibiofilm activities against *S. aureus*. ZnO NPs synthesized by a simple, non-toxic method using fungal filtrate of *Xylaria acuta* were promising antimicrobial agents that

Table II. The antibacterial properties against *S. aureus* of green-synthesized ZnO NPs.

First author/s, year	Material type	Material	ZnO NPs size	ZnO NPs shape	Bacterial strain	MIC	ZOI	(Refs.)
Mohammed *et al*, 2023	Plant	*Cymbopogon citratus*	20-24 nm	Hexagonal rod-like	*S. aureus* (MTCC 9760)	88.13±0.35 µg/ml	19.60±0.66 mm	(56)
Mushtaq *et al*, 2023		*Viscum album*	13.5 nm	Quasi-spherical	*S. aureus* (ATCC 29213)		40±0.3 mm	(57)
Al-Askar *et al*, 2023		*Pluchea indica*	21.9 nm	Spherical	*S. aureus*	250 µg/ml	17.0±1.0 mm	(146)
Hasan *et al*, 2022		*Withania coagulans*	25 nm	Flower-shaped	*S. aureus*	1.25 µg/ml	21 mm	(58)
Ting *et al*, 2022		*Andrographis paniculata*	<98.61 nm	Flower-shape	*S. aureus* (ATCC 29737)		25 mm	(53)
Irfan *et al*, 2022		*Acacia modesta*	70±03 nm	Rod	MRSA		16±0.02 mm	(59)
Malhotra *et al*, 2023		*Eupatorium odoratum*	50 nm	Spherical and hexagonal	*S. aureus* (MTCC87)	250 µg/ml		(61)
Alallam *et al*, 2023		Curcumin	27.61±5.18 nm	Grain-shaped and spherical	*S. aureus*	500 µg/ml	10.60±0.10 mm	(60)
Kahandal *et al*, 2023		Locust Bean Gum	20-40 nm	Spherical	*S. aureus* (ATCC 6538)	125 µg/ml		(36)
Sachin *et al*, 2023		Lychee	<10 nm	Spherical	*S. aureus*	500 µg/ml	15.0 mm	(55)
Doğaroğlu *et al*, 2023		*Mentha spicata*	24.5 nm	Triangular	*S. aureus* (ATCC 25923)		17.83 mm	(54)
Doğaroğlu *et al*, 2023		*Ocimum basilicum*	26.7 nm	Triangular	*S. aureus* (ATCC 25923)		16.14 mm	
Manojkumar *et al*, 2023		*Brassica oleracea*	52 nm	Flower-like	*S. aureus*		13 mm	(147)
Irfan *et al*, 2021		*Psidium guajava Linn*	41.34 nm	Hexagonal	*S. aureus*		12±0.23 mm	(148)
Jamil *et al*, 2020	Algae	Microalgae strain ZAA1 (MF140241) ZAA2 (MF114592) ZAA3 (MF114594)	1-100 nm	Spherical	*S. aureus*		14.5 mm 20 mm 14 mm	(63)
Lopez-Miranda *et al*, 2023		*Sargassum*	20-200 nm	Irregular	*S. aureus* (ATCC 6538)	800 µg/ml		(66)
Morowvat *et al*, 2023		*Chlorella vulgaris*	33.4 nm	Rod	MRSA	400 µg/ml		(64)
Ebadi *et al*, 2019		cyanobacterium *Nostoc sp. EA03*	50-80 nm	Star-shaped	*S. aureus* (ATCC 25923)	64 µg/ml		(68)
Ebadi *et al*, 2022		cyanobacterial strain *Desertifilum sp. EAZ03*	88 nm	Rod	*S. aureus* (ATCC 59223)	32 µg/ml		(67)

Table II. Continued.

First author/s, year	Material type	Material	ZnO NPs size	ZnO NPs shape	Bacterial strain	MIC	ZOI	(Refs.)
Alsaggaf *et al*, 2021		*Ulva fasciata Delile*	77.81 nm	Flower and sphere shapes	*S. aureus* (ATCC 25923)	22.5 µg/ml	19.7±1.1 mm	(65)
Mohd Yusof *et al*, 2020	Bacteria	*Lactobacillus plantarum TA4*	291.1 nm	Flower-like (ZnO NPs-CFS)	*S. aureus*	1250 µg/ml	16.5 mm	(71)
			191.8 nm	Irregular (ZnO NPs-CB)		312.5 µg/ml	16 mm	
Shaaban and El Mahdy *et al*, 2018		*Streptomyces* isolate S12	20-50 nm	Spherical	*S. aureus* (ATCC 29213)	200 µg/ml		(73)
					MRSA clinical isolates	3.25-50 µg/ml		
Rehman *et al*, 2019		*Bacillus haynesii* (GeneBank: MG822851)	50±5 nm	Spherical and a few rod-shaped	*S. aureus* (ATCC 29213)	4 mg/ml		(72)
Taran *et al*, 2018		*Halomonas elongata* IBRC-M 10214	18.11±8.93 nm	Spherical	*S. aureus* (ATCC 43300)	13.6 µg/ml		(74)
Kang, 2022		*Leuconostoc sp. Strain C2*	173.77± 14.53 nm	Rod	*S. aureus*	512 µg/ml		(76)
Abdo *et al*, 2021		*Pseudomonas aeruginosa*	14.95±3.5 nm	Spherical	*S. aureus* (ATCC 6538)	200 µg/ml	12.33±0.9 mm	(149)
Sharma *et al*, 2021	Fungi	*Phanerochaete chrysosporium*	50 nm	Hexagonal	*S. aureus* (MTCC-96)	0.1 µg/ml	23 mm	(77)
Mohamed *et al*, 2021		*Penicillium chrysogenum*	9-35 nm	Hexagonal	*S. aureus* (ATCC 23235)	2 mg/ml	16.33±0.88 mm	(78)
Sumanth, 2020		*Xylaria acuta*	34-55 nm	Hexagonal	*S. aureus* (NCIM No. 2079)	15.6 µg/ml		(79)
Abdelkader *et al*, 2022		*Aspergillus niger*	31.75±4.38 nm	Spherical morphology with some hexagonal architecture	*S. aureus* (ATCC 29231)	8-128 µg/ml		(80)
Motazedi *et al*, 2020		*Saccharomyces cerevisiae*	<30 nm	Spherical	*S. aureus* (ATCC 25923)		25 mm	(81)

ZnO NPs, zinc oxide nanoparticles; *S. aureus*, *Staphylococcus aureus*; MRSA, Methicillin-resistant *Staphylococcus aureus*; CFS, the cell-supernatant; CB, the cell-biomass; MIC, minimum inhibitory concentration; ZOI, zone of inhibition.

exhibited an MIC value of 15.6 μg/ml against *S. aureus* (79). Abdelkader *et al* (80) synthesized ZnO NPs using *Aspergillus niger Endophytic* fungal extract with characteristics of stability and antibiofilm activity. It was demonstrated that ZnO NPs reduced the number of biofilm-forming *S. aureus* from 50-20.83% and the MIC of ZnO NPs against multiple *S. aureus* strains ranged from 8-128 μg/ml (80). In Motazedi *et al* (81), the extracellular extract of *Saccharomyces cerevisiae* was used to create spherical ZnO NPs with dose-dependent antibacterial ability against *S. aureus*.

4. ZnO NPs cooperating with antibiotics for *S. aureus* treatment

At present, one of the most serious issues of global health must be antibiotics resistance. The synergy between antibiotics and ZnO NPs attracts much attention and would be a practicable treatment against multi-drug resistant bacteria (82,83). It has been found that ciprofloxacin in conjunction with ZnO@ Glu-TSC (thiosemicarbazide-conjugated and glutamic acid-functionalized ZnO NPs) could significantly inhibit the expression of efflux pump genes, which is a vital factor towards antibiotics resistance (84). In addition, ZnO NPs can be excellent drug carriers to target antibacterial agents to the action sites and still achieve desired therapeutic effects for a decreased drug dosage, thus enhancing the antimicrobial efficacy (22). In Habib *et al* (85), using ZnO NPs combined with ciprofloxacin and imipenem, the ZOI of *S. aureus* was 17 mm higher than that of *E. coli* (12 mm). By using ZnO NPs in conjunction with antibiotics to defeat *S. aureus*, the MICs of six clinical common antibiotics were reduced, which reflected an effective antibacterial cooperation. Furthermore, the anti-biofilm efficacy was also investigated and was enhanced from 34-37% (antibiotics alone) to 65-85% (antibiotics and ZnO NPs combination) (86).

Hemmati *et al* (87) synthesized and characterized the chitosan-ZnO nanocomposites loading with gentamicin, which caused MIC reduction by four-fold and biofilm reduction by 77% in *S. aureus* by contrast with the gentamicin alone. Notably, drug-loaded ZnO NPs were shown to exhibit negligible toxicity to human cells (82). Thus, the synergy of ZnO NPs and antibiotics can be applied to a variety of antibacterial circumstances. In an infection model of rats, azithromycin-loaded ZnO NPs displayed enhanced ability to clear MRSA (88). Phytomolecules-coated ZnO NPs combined with tobramycin and gallic acid were synthesized and shown to be an excellent material for contact lenses, expressing a maximum $\log_{10}$ reduction of 5.7±0.02 CFU/ml in the growth of *S. aureus* and contributed to disruption of bacterial cell wall and membrane, leading to the leakage of cytoplasm and bacterial death (89). These drug-hybrid NPs such as cefazolin-hybrid ZnO NPs are also used to post-operative antimicrobial therapy due to their inhibitory actions against *S. aureus* both *in vitro* and *in vivo* (90).

5. ZnO nanocomposites/hybrids against *S. aureus*

Non-metal ZnO nano-composites/hybrids against S. aureus. In order to improve the antibacterial activity of ZnO NPs, various non-metal substances have been used to prepare ZnO nanocomposites. In Oves *et al* (91), the combination of graphene, curcumin and ZnO NPs showed enhanced inhibition against *S. aureus* more than five-fold compared with graphene-ZnO NPs and the ZnO nanocomposites also suppressed MRSA (ATCC 43300) effectively. Zhai *et al* (92) designed ZnO-graphene nanocomposites that could enhance rapid antibiosis due to the separation of ZnO electron-hole pairs and increased active sites by transforming the shape of ZnO. Silica nanorattles (SNs) combined with ZnO NPs were reported to exhibit an improved antibacterial activity against MRSA with a lower MIC of 6.25 μg/ml compared with free ZnO NPs *in vitro* and *in vivo*. Since the SNs surface protected and amassed the ZnO NPs, the free radicals offered by ZnO NPs had an enhanced efficacy in combating MRSA (93). Vinotha *et al* (94) developed the Btp-Ac-ZnO nanocomposites by using *Acorus calamus* extract and bacterial toxic protein (Cry) and they demonstrated the concentration-dependent biofilm inhibition of the synthesized nanocomposites against *S. aureus* (MTCC 9542). ZnO NPs can also be supported by 4A zeolite, controlling the release of ZnO NPs and enhancing the antibacterial properties (95). It has been shown that pancreatin-doped ZnO nanocomposites have improved performances, such as low-toxicity to human cells and anti-biofilm and anti-motility abilities against MRSA and increased sensitivity for vancomycin against MRSA (96). Canales *et al* (97) demonstrated that the electrospun scaffolds based on poly (lactic acid), bioglass and ZnO NPs showed biocidal properties against *S. aureus* with bacteria decreasing by 30%, which may be useful for tissue engineering. Hydroxypropyl methylcellulose film combined with ZnO NPs and carboxymethyl starch have been shown to have excellent antibacterial ability against *S. aureus* and no toxicity to human HaCat cells and so can be used for wound dressing (98). Majeed *et al* (99) found that ZnO NPs doped with selenium showed strong inhibition to MRSA, however, teratogenicity was also revealed, which means that it is important to use them cautiously.

Nano-hybrids are also recommended as a good replacement for conventional antibacterial ZnO NPs and have enhanced antibacterial efficacy and low-toxicity on normal cells (100). According to Karthikeyan *et al* (101), in order to develop nanomaterials with high antibacterial ability compared with antibiotics, the alginate-ZnO hybrid nanomaterials have been synthesized with good inhibition effects on MRSA and low cytotoxicity to human cells. Kang *et al* (102) reported that the dispersibility of ZnO could be improved by the hybridization of ZnO NPs with nanocellulose and increasing bacterial inhibition rates were shown in *S. aureus*. Furthermore, in the research of AbouAitah *et al* (103), a hybrid nano-formulation was developed from ZnO NPs and protocatechuic acid and offered a sustained-release antibacterial effect toward *S. aureus* (Fig. 4).

Metal-doped ZnO nanocomposites against S. aureus. The activities of metal ions can be improved by the amalgamation of metal NPs. For instance, the release of more zinc and copper ions has been confirmed by ICP-OES analysis in Cu-doped ZnO nanocomposites, which caused enhanced antibacterial activity against *S. aureus* (104). In Rao *et al* (105), Na-doped ZnO NPs expressed enhanced inhibition activity against *S. aureus* with Na-concentration dependence. By using a scaled-up green

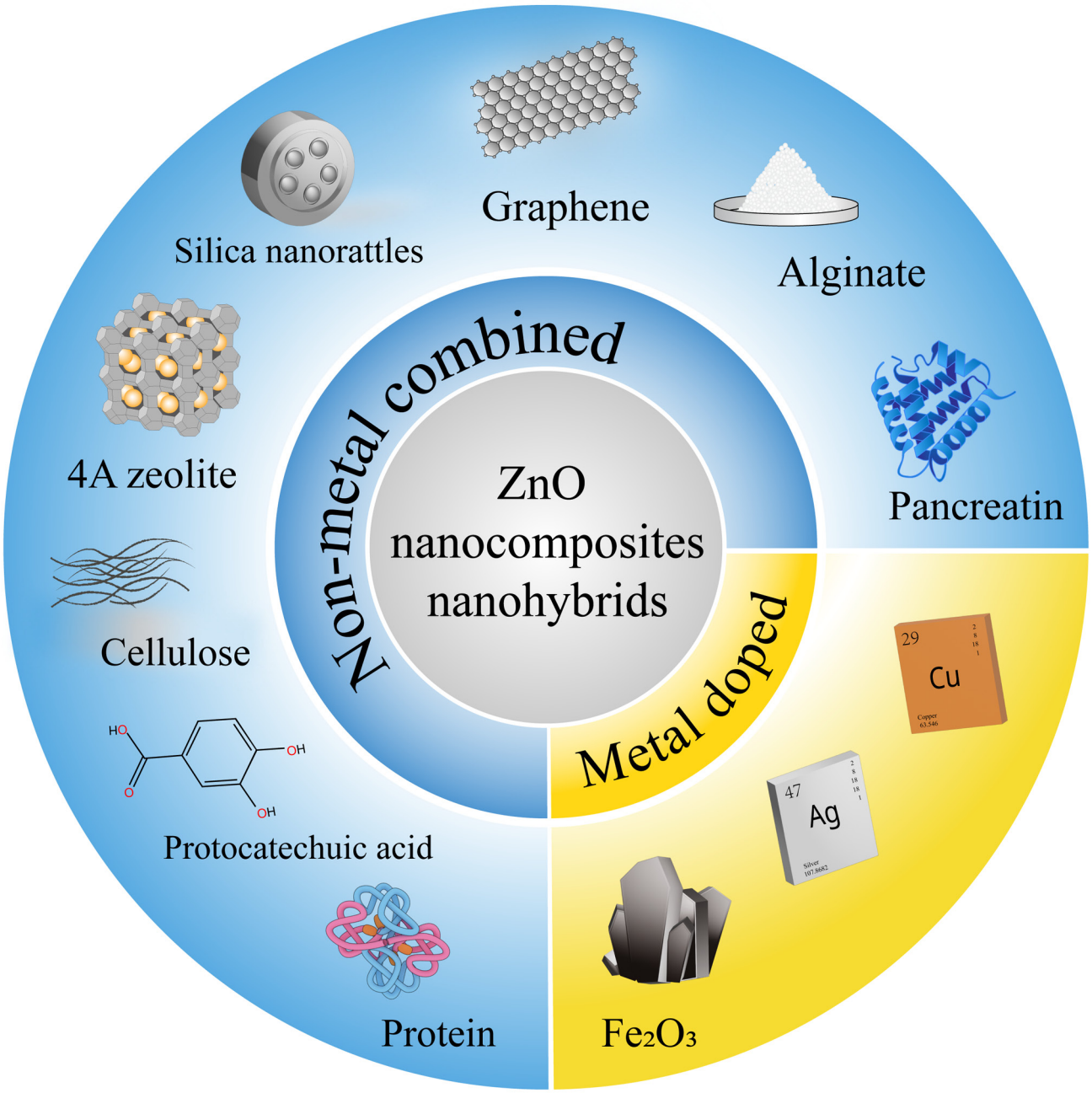

Figure 4. Substances that combined with ZnO NPs were used to make ZnO nanocomposites/nanohybrids. ZnO NPs, zinc oxide nanoparticles.

strategy, cellulose-based Ag-ZnO nanocomposites (AZC) were prepared, which demonstrated good stability. It was also reported that the AZC films showed greater inhibition against *S. aureus* than *E. coli* (106). Hu *et al* (107) revealed that ZnO/Ag bimetallic nanocomposites showed significant inhibition against *S. aureus* compared with single metal nanomaterials and the cytotoxicity to fibroblasts was reduced by a ZnO and Ag complex. Mohammadi-Aloucheh *et al* (108) reported that ZnO/CuO nanocomposites synthesized using fruit extracts could lead to the disruption of bacterial membranes and enhanced anti-bacterial ability compared with ZnO NPs alone. Bahari *et al* (109) synthesized Fe_3O_4/ZnO nanocomposite by the sol-gel method and the molar ratio of 1:10 showed the best antimicrobial performance against *S. aureus* with a ZOI of 11.5±0.7 mm. AlSalhi *et al* (110) used the co-precipitation technique to make magnetic ZnO/$ZnFe_2O_4$ nanohybrids that were good photocatalytic material and it was discovered that the membrane of *S. aureus* collapsed after exposure to the nanohybrids. Lee *et al* (111) made a multi-metal oxide nanocomposite including ZrO, ZnO and TiO_2. It was observed that these nanocomposites demonstrated a killing efficiency of 72.4% against *S. aureus*. Poly (vinyl alcohol)-based compositions were developed with addition of silver, copper and ZnO NPs, which had the feature of solidifying to be peeled off along with the impaired bacterial film, thereby decreasing the number of *S. aureus* (112).

6. Functional ZnO NPs for *S. aureus* treatment

In order to optimize the performance of ZnO NPs to combat pathogenic microorganisms, researchers have given attention

to functionalized, modified or capped ZnO NPs (34,113). Choi *et al* (114) created novel ZnO NPs functionalized with caffeic acid, which expressed enhanced antibacterial efficiency against *S. aureus* and three MRSA strains. The amino-functionalized hydrophilic ZnO NPs induced the destruction of respiratory electron transformation, generation of intracellular ROS and depolarization of cell membrane in *S. aureus* (115). Charoensri *et al* (116) prepared polyaniline-functionalized ZnO NPs by a simple impregnation method; not only did the synthesized ZnO NPs films show enhanced water hydrophobicity, but also expressed increased antibacterial ability against *S. aureus*, which will make it possible to develop antibacterial biodegradable materials. Lee *et al* (117) prepared gallic acid functionalized ZnO NPs that had high bacterial cell membrane affinity and showed enhanced bactericidal activity against *S. aureus* and higher selective inhibition to MRSA strains compared with non-functionalized ZnO NPs. According to Chen *et al* (118), photosensitizers-functionalized ZnO NPs demonstrated marked *S. aureus* inhibition and showed low-toxicity on endothelial cells and erythrocyte. In Yuan *et al* (119), lysozyme-modified ZnO NPs expressed excellent antibacterial activity against *S. aureus* and MRSA due to their small size, membrane permeability and enzyme-mediated ROS generation and even had lower cytotoxicity than gentamycin at the same concentration.

7. Conclusion and perspectives

In the present study, ZnO NPs synthesized by different methods and their antibacterial activity against *S. aureus* have been summarized. Taken together, the anti-*S. aureus* efficacy of ZnO NPs mainly relies on their basic characteristics, especially size and shape. Spherical shape and small size are ideal features of ZnO NPs to combat bacteria that lead to high specific surface areas and more chances to contact with pathogens. In Babayevska *et al* (24), ZnO NPs with the highest specific surface area showed the size <10 nm. It is also reported that spherical ZnO NPs had the minimal size (31 nm) and higher anti-*S. aureus* activity (6-7 log CFU ml^{-1} reduction) compared with flower-shaped particles (3-4 log CFU ml^{-1} reduction for *S. aureus*) (44). The detail of ZnO NPs synthesized by various physical and chemical methods has been the subject of recent research (40). Some studies also revealed that these traditional synthesized methods had various shortcomings, such as being environment-contaminating, expensive and energy-intensive (43,120,121). Green synthesis has been emphasized due of its environment-friendly, easy-acquired and low-toxicity features. Some studies also noted that these green materials had antibacterial abilities already, such as mint (122), aloe (123) and curcumin (124), and they endow ZnO NPs with enhanced and steady antibacterial activity against *S. aureus* (125). Physical or chemical processes are the indispensable part in NPs synthesis. However, ZnO NPs made only by physicochemical ways are cannot compare with biogenic, functional or compound ZnO NPs when they are further applied to clinical antibacterial situations.

ZnO NPs can be used in a number of pre-clinical and clinical antimicrobial fields, including surgical operation (59), post-operative anti-bacterial therapy (90), anti-inflammatory (80) and ophthalmic treatment (126). For example, suture coated by green synthetic ZnO NPs demonstrated excellent tensile strength and wound healing ability in an incision wound rat model (59). An infection model in mice showed that ZnO NPs originating from fungi could significantly decrease hepatic inflammatory markers, restrain congestion and fibrosis in tissues and improve liver function (80). Sindelo *et al* (127) made the phthalocyanines link to the amino-functionalized ZnO NPs and these nanocomposites showed considerable activities of photodynamic antimicrobial chemotherapy and multi-microbial biofilms eradication. Considering that ZnO NPs had an excellent antibacterial activity against *S. aureus* and good biocompatibility, a chitosan-ZnO/selenium nanoparticles scaffold was developed to be used for infected wound healing and postoperative treatment of pediatric fractures (128). Ismail *et al* (129) also reported that ZnO NPs could be used as the hand sanitation in the future, which present improved anti-MRSA activity compared with the commonly used alcohol sanitation.

As one of the primary metal oxide NPs, ZnO NPs express excellent ability against *S. aureus*, but they still have drawbacks to be widely used as antibiotics replacements in clinical contexts. A few trials *in vivo* suggested that different metal oxide NPs damage cells to different degrees (45). Venkatraman *et al* (130) noted the toxicity of ZnO NPs to RAW264 macrophage cells, with half maximal inhibitory concentration (IC_{50}) of 494 μg/ml. Although electrospun scaffolds based on ZnO NPs showed increasing antibacterial activity, it is also reported that cytotoxicity was related to high ZnO content (97). According to Pereira *et al* (131), erythrocyte changes were also discovered in reptile exposure to ZnO NPs at the dose of 440 μg/kg. Yang *et al* (132) reported that ZnO NPs could induce apoptosis of mouse-derived spermatogonia cell line GC-1 spg cells. In Al-Zahaby *et al* (133), ZnO NPs (0.69 mg/l) mediated ROS that induced cell apoptosis and caused sensory toxicity effect on zebrafish olfactory organs. ZnO NPs synthesized by *Calotropis procera* leaf extract were reported to exhibit potent antimicrobial ability with concentration-dependent manner. However, with increasing exposure to ZnO NPs, deleterious changes (degeneration, swelling and atrophy) were found in the kidney by histology (85). Nazir *et al* (134) also discovered liver dysfunction in mice intraperitoneal injection groups at ZnO NPs doses of 50 and 100 mg/kg. ZnO NPs were also cytotoxic to the human immune system at doses of 25 and 12 mg/l (135). Despite ZnO NPs exhibiting outstanding capability in inhibiting MRSA, the resistance to NPs by microbes remained. If the dosage of NPs is below the sublethal concentrations, a series of resistance mechanisms would be initiated stealthily by bacteria, resembling their antibiotic resistance (136).

ZnO NPs still have potential toxicity when they are applied to clinical antibacterial treatment, though green-ZnO NPs have shown lower cytotoxicity than physicochemically synthesized ZnO NPs (60). Studies mostly pay close attention to the improving methods for preparation of ZnO NPs (42,48,54). They focus on the physical characteristics and antibacterial abilities, but neglect, to some degree, the cytotoxicity tests *in vivo*. Markedly, researchers have developed a predictive model to evaluate the security of ZnO

NPs with different features and the authors point out that ZnO NPs with larger size, spherical shape, negative charge and a higher tendency for aggregation are safer, which is of great value to further toxicity studies (137). Notably, ZnO NPs <100 μg/ml were biocompatible and the cytotoxicity was parallel with their antibacterial activity, which meant that the anti-*S. aureus* mechanism (direct contact to cells, ROS and Zn^{2+} releasing) was also the potential killing process in normal cells (24). Although a number of reports explained the antibacterial mechanism against *S. aureus* of metal and metal oxide NPs, the studies for ZnO NPs were still limited compared with other metal NPs such as Ag NPs (26,138). The majority of ZnO NPs anti-*S. aureus* properties lack a comprehensive assessment and were only analyzed by well or disc diffusion test and bacterial growth curve and some studies only reported ZOI or MIC or even neither of them (42,50,126). A uniform standard of *S. aureus* strain is also necessary, which would play a crucial role in comparing antibacterial effects of ZnO NPs made by different methods.

In order to restrict the immoderate proliferation and mutation of pathogens, unremitting efforts should be made to optimize antibacterial strategies. As aforementioned, the synergism of ZnO NPs and other materials showed complemental effects, enhanced antibacterial activity and improved properties in clinical applications. Due to technology developments, there are more potentials for ZnO NPs preparation and biomedical application. For instance, apart from the green synthesis aforementioned, material-saving, safe and even granular NPs can be made by more novel methods, such as microfluidic (120). Except for using green and easily obtained raw materials, synthetic methods should be able to flexibly control the size, shape and dispersity of ZnO NPs, which means that the key material and procedure of ZnO NPs synthesis must be identified by modern techniques. Notably, genomic and proteomic techniques should be devoted to the exploration of the antibacterial mechanism, synthesis optimization and cytotoxicity of ZnO NPs. The antibacterial study of effects at the cellular level in the long term is an essential component to investigate the dosage and safety of ZnO NPs. It is necessary to focus on ZnO NPs studies *in vivo*, especially the biokinetics, bioavailability, tissue distribution and clearance rate, which are essential for their antibacterial applications and improved using as antibiotics replacements. In addition, composite and functional ZnO NPs could enhance the antibacterial advantages to some degree and decrease their toxicity and also reduce the excessive exposure of ZnO NPs that diminish the possibility of antimicrobial resistance, this is for future researchers.

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Authors' contributions

HY and GD conceived the present study. YH, YW, LZ, FL, YJ, JL and SC performed the literature search, drafted the manuscript and drew the figures. YH wrote the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

Authors' information

Optional

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