Nickel Nanoparticles

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Methicillin-resistant Staphylococcus aureus (MRSA) has evolved vast antibiotic resistance. These strains contain numerous virulence factors facilitating the development of severe infections. Considering the costs, side effects, and time duration needed for the synthesis of novel drugs, seeking efficient alternative approaches for the eradication of drug-resistant bacterial agents seems to be an unmet requirement. Nickel nanoparticles (NiNPs) have been applied as prognostic and therapeutic cheap agents to various aspects of biomedical sciences. Their antibacterial effects are exerted via the disruption of the cell membrane, the deformation of proteins, and the inhibition of DNA replication. NiNPs proper traits include high-level chemical stability and binding affinity, ferromagnetic properties, ecofriendliness, and cost-effectiveness. They have outlined pleomorphic and cubic structures. The combined application of NiNPs with CuO, ZnO, and CdO has enhanced their anti-MRSA effects. The NiNPs at an approximate size of around 50 nm have exerted efficient anti-MRSA effects, particularly at higher concentrations. NiNPs have conferred higher antibacterial effects against MRSA than other nosocomial bacterial pathogens. The application of green synthesis and low-cost materials such as albumin and chitosan enhance the efficacy of NPs for therapeutic purposes.

Keywords: methicillin-resistant Staphylococcus aureus ; nickel nanoparticles ; antibacterial effects

1. Introduction

Staphylococcus (*S.*) *aureus* is a ubiquitous pathogenic bacterium. Methicillin-resistant *S. aureus* (MRSA) is among the leading causes of nosocomial pathogens which decipher the multidrug-resistance (MDR) phenotype [1][2][3]. MRSA employs various mechanisms to resist drugs, such as cell wall thickening, efflux of compounds, enzymatic destruction, and target variation [4][5][6].

MRSA infections encompass a wide range of manifestations and are a major life-threatening priority worldwide [7][8]. MRSA is resistant to β-lactam antibiotics. These strains carry a modified penicillin-binding protein (PBP) known as PBP-2a (encoded by either *mecA* or *mecC* gene) inherently exhibiting resistance to various β-lactams such as oxacillin, methicillin, and cefoxitin [9]. MRSA is classified based on genotypic diversity and according to various staphylococcal cassette chromosome *mec* (SCC*mec*) types including SCC*mec* (I-XIII) as substantial markers of MRSA epidemiology. The SCC*mec* gene cassette carries the *mecA* or *mecC* genes in addition to other genes associated with aminoglycosides, macrolides, and fluoroquinolones resistance [10]. MRSA is classified into three main categories including healthcare (HA-MRSA), community (CA-MRSA), and livestock-associated (LA-MRSA) strains each with special virulence and resistance patterns [7][10]. HA-MRSA is responsible for nosocomial infections globally and usually carries SCC*mec* types I, II, or III. CA-MRSA has been recorded in patients without or by negligible contact with healthcare settings. These strains usually carry SCC*mec* elements IV, V, and *pvl* genes. The latter is associated with the Panton–Valentine leukocidin. The LA-MRSA isolates are mainly associated with livestock origins and usually carry SCC*mec* IVa and SCC*mec* V elements. Life-threatening infections caused by LA-MRSA have been previously recorded, highlighting the possibility of zoonotic risk [11][12]. In humans, MRSA can cause severe pyogenic infections of the skin and soft tissue, endocarditis, septic arthritis, pneumonia, osteomyelitis, and otitis media [9][13].

2. Pathogenicity of MRSA

Although the colonization of *S. aureus* on host surfaces is not harmful, overcoming the host's innate immunity leads to invasive deep infections. MRSA causes various cutaneous and deep infections such as folliculitis, impetigo, cutaneous abscesses, pyomyositis, necrotizing pneumonia, and fasciitis [14]. HA-MRSA causes implant or surgical site and catheter-associated infections. Bacteremia-related infections include disseminated infections such as descending urinary tract infections, endocarditis, and osteomyelitis. Thereby, the eradication of the bacterium is a concern considering recurrent infections. The bacterium virulence regulation is exerted by a set of global regulatory circuits (two-component systems,

TCS, accessory gene regulatory, Agr, and quorum-sensing, QS) which affect gene expression following environmental signals. Additionally, *S. aureus* responds to internal stimuli in the form of QS autoinduced signaling. AgrBDCA regulates RNA effector RNAIII [15][16].

Biofilm formation is an indispensable mechanism of resistance to antimicrobials and for the environment of host responses. The polysaccharide intercellular adhesin (PIA) mediates the bacterial binding to host cells. Some other major surface adhesin proteins include fibrinogen binding protein (FnBP) A and B, surface binding protein A (Spa), cell wall-anchored proteins (CWP), clumping factors (Clfs) A and B, and surface binding protein (SasG) [17][18][19][20].

Following the bacterial attachment to the cells and colonization, pathogenesis is initiated and developed via the production of toxins, exoenzymes such as exfoliative toxins (ETs), Panton–Valentine leukocidin (PVL), toxic shock syndrome toxin1 (TSST1), phenol-soluble modulins, leukotoxin and haemolysin, lipases, proteases and nucleases, and immunomodulators or immune evasion gene clusters (IEC1 and IEC2) [21].

Phenol-soluble modulins, leukotoxin, and haemolysin are known as pore-forming toxins which lyse the host cells. α-, β-, γ-, and δ-hemolysins of *S. aureus* cause the lysis of erythrocytes, epithelial and endothelial cells, monocytes, damage of the epithelium, and induction of apoptosis. Leukotoxins or PVL target and destroy white blood cells such as macrophages, monocytes, and neutrophils. These include LukDE, LukAB, LukS-PV, and LukF-PV. PVL is associated with soft tissue and skin infections in both MSSA and MRSA [22][23].

Phenol-soluble modulins (PSMs) including PSMα1–PSMα4 play a substantial role in bacterial pathogenesis via cell lysis, inflammation, immune regulation, and biofilm formation or detachment [24]. Exfoliative toxins (ETA-ETD) cause staphylococcal scaled skin syndrome (SSSS) which is associated with dehydration, loss of superficial skin layers, and secondary infections which are not significantly different from MSSA and MRSA [25]. Staphylococcal enterotoxins (SEs) and TSST-1 act as superantigens which are T-cells mitogens. SEs cause food poisoning and gastrointestinal problems such as emesis. TSST1 causes the release of extraordinary amounts of pro-inflammatory cytokines [26]. In addition to humans, MRSA has long been recognized globally to colonize numerous wild and domesticated livestock animals and develop infections [27][28][29][30][31]. The widespread distribution of MRSA among livestock is largely due to the indiscriminate prescription/consumption of antimicrobials for animal breeding or agricultural activities. For example, it has impacted more than 40% of pig farms, 20% of cattle farms, and 20% to 90% of turkey farms in Germany. Numerous studies have shown that there is a high risk of MRSA colonization and infection in humans who come into contact with livestock [32][33]. MRSA is repeatedly recorded in dairy farms as a cause of mastitis with failure in elimination due to its resistance against β-lactam antibiotics employed for related infections [34].

MRSA strains employ various virulence factors to invade the host and develop resistance [6]. The development of resistance to last-resort antimicrobial treatments such as glycopeptides (vancomycin and teicoplanin) is a crisis in the eradication of vancomycin-intermediate *S. aureus* (VISA) or vancomycin-resistant *S. aureus* (VRSA) [17][35]. For skin infections (impetigo) of MRSA, mupirocin and fusidic acid or alternative 1% hydrogen peroxide (H_2O_2) are recommended. For abscesses, in conditions of neutropenia, cell-mediated immunity deficiency, or severe infection, there is a need for co-trimoxazole or clindamycin treatment. For cellulitis and soft tissue infections, glycopeptides, tigecycline, and linezolid are useful. Susceptibility testing is strongly recommended prior to the utilization of antimicrobial drugs. Antimicrobial therapy necessity should be evaluated when infections are observed due to costs and risk of resistance evolution. The term “superbug” is defined as a strain developing vast antibiotic resistance [36].

Combination therapies have demonstrated substantial bactericidal effects against MRSA. The combination of carbapenems with linezolid, and each of imipenem/fosfomycin/gentamicin/oxacillin/rifampin and daptomycin have deciphered acceptable anti-MRSA effects [37][38][39]. A β-lactams and daptomycin combination facilitates its binding and mitigates resistance development [40][41]. Additionally, the combination of gentamicin/β-lactams/rifampin and vancomycin has outlined significant effects [42][43]. However, the combination of vancomycin and β-lactams has had nephrotoxicity according to clinical trials [44][45][46].

Natural combination therapies using Polysporin and Neosporin peptides have also exerted anti-MRSA effects [47]. Major chemotherapy approaches to combat MRSA have included telavancin, teicoplanin, ceftaroline, vancomycin, and oxazolidinones [48][49]. The combination of β-lactam and either arbekacin or vancomycin is recommended against MRSA. Notably, granulocyte counts are also recommended for antibiotics consumption [50][51]. Ceftaroline fosamil has exhibited substantial anti-MRSA effects [52][53][54]. Daptomycin and ceftaroline have exhibited higher bactericidal effects and linezolid has exerted strong effects on bacteremia.

As the first clinically applied anti-MRSA oxazolidinones, linezolid is a promising antibiotic with low resistance development to MRSA. However, epidemiological data have unraveled that linezolid resistance among MRSA isolates is in enhancement alongside novel antimicrobials quinupristin/dalfopristin (Q/D), daptomycin, and tigecycline [55][56]. Major drawbacks in the conventional approaches to MRSA eradication using antibiotics include non-specific effects which kill human beneficial bacteria, adverse/toxic effects, drug resistance development, and the high cost and time-consuming development of new drugs.

3. Nanoparticle Applications to Combat MRSA

The efficient, non-toxic, proper, accurate, and cost-effective eradication of MRSA infections has been recently achieved through the application of nanocarriers or nanoparticles (NPs) [57][58]. NPs have a size range of 1 to 100 nm. The physicochemical properties of NPs and lower costs are gaining attention for use as antimicrobial agents [59][60][61][62]. NPs have exhibited antimicrobial effects, particularly those synthesized using green methods [6]. NPs can also be used for the detection of MRSA [63]. The main mechanisms of NP antibacterial effects include an impairment in metabolism or bacterial integrity (CuNPs), replication and transcription disruption, tRNA, ATPases, membrane-bound enzymes and biofilm inhibition, protein denaturation (AgNPs), and reactive oxygen species (ROS) production [64][65][66]. Various NPs such as silver (Ag), gold (Au), and lower-cost NPs such as nickel (Ni), titanium-oxide, (TiO), zinc oxide (ZnO), silica (SiO2), and bismuth (Bi) NPs have deciphered efficient bactericidal effects against MRSA in vitro and in vivo [67][68][69][70][71]. Various methods of NP delivery to cells for antibacterial activity include polymeric NPs, liposomes, carbon NPs, and metal or metal-oxide NPs. ZnO could eliminate MRSA skin infection at 1875 mg/mL possibly via amino acid synthesis inhibition [70]. TiO2 NPs produce free radicals which kill MRSA [72]. Cu-doped ZnO nanorods have exhibited more potential effects than that of ZnO singly [73]. Cefotax-based magnetic NPs have exhibited promising anti-MRSA effects against isolates originating from livestock and dairy sources [58]. Interestingly, S,N-GQDs/NiO nanocomposites have exerted extraordinary anti-*S. aureus* effects in vitro with minimum inhibitory (MIC) and bactericidal (MBC) concentrations values of 0.4 and 0.8 mg/mL, respectively [74]. Nickel oxide nanoparticles (NiO NPs) exhibit promising traits such as biocompatibility, thermal and chemical stability, and interesting optical characteristics. The development of NiO nanocomposites has improved their bactericidal effects. The simple synthesis of a CdO–NiO–ZnO nanocomposite using the microwave method also exhibited antibacterial effects against Gram-positive and Gram-negative species [75][76]. In addition, NiOCuO-10%RGO also demonstrated substantial antibacterial activity [74]. NPs can specifically carry drugs and enter into cells via endocytosis. A few NPs for the eradication of MRSA have been used for clinical trials. PLGA-rifampicin NPs have decreased the MIC against MRSA from 0.0008 to 0.002 µg/mL [77]. Vancomycin-loaded hydroxyapatite increased the vancomycin release and improved bone regeneration [78]. The combination of levofloxacin and AgNPs unraveled a synergistic effect with 0.5 and 10 µM against control strains and MRSA, respectively [79]. The application of liposome-albumin-vancomycin has decreased toxicity and improved the anti-MRSA activity [80].

It was revealed that Chitosan/Gold Nanoparticle/Graphene Oxide could separate, identify, and eradicate MRSA superbugs within water contaminants. Chitosan has a positive charge and can trap these strains. In a study by Gupta, engineered polymer NPs exerted anti-biofilm effects against MRSA strains at non-toxic levels [81].

Mesoporous silica nanoparticles (MSNs) carrying enzymes have exhibited anti-biofilm (dispersal) effects against *S. aureus*, decreasing the bacterial cells efficiently after 24 and 48 h [82], respectively.

4. Importance of Nickel and Nickel-Oxide Nanoparticles

Nickel nanoparticles (NiNPs) including magnetic metal intermediate-cost particles have been studied vastly thanks to their myriad applications such as for magnetic sensors [83], memory devices [84], and for biomolecular separation [85]. The eventual proficiency of each material or NP reflects and depends on the structure, shape, size, and purity of NiNPs or derived materials. Nickel oxide (NiO) is an inevitably crucial part of today's nanotechnology and intermediate-cost metal oxide is a cubical lattice structure [86]. The extraordinary chemical stability, high binding affinity, and ferromagnetic properties of NiNPs provide an indispensable field of study which includes their synthesis and application. They are applied mostly because of cost-effectiveness catalysts considering vast natural resource existence and driving reactions by alternate routes. These NPs contain numerous biomedical usages, including cell isolation, medicine delivery, magnetic resonance imaging, biomedical diagnostics, and more [87]. Considerable antibacterial attributes have been reported against *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *S. aureus*, and many other microorganisms [88].

5. Mechanism of Action of Nickel Nanoparticles

Antibacterial activities of NiNPs are related to nickel ion content which interpenetrate the bacterial cell and reach the surface of the bacterial cell membrane and intracellular milieu. This influx of nickel cations destroys organelles like ribosomes and affects bacterial metabolism. A study of the literature unravels how all of this happens, due to electrostatic attraction and the use of negatively charged intercellular microbial cells and positively charged nickel ions [89][90]. Nanoparticles exhibit great surface activity due to the large surface-to-volume proportion. Exposure of *E. coli* to NiNPs disrupts membrane morphology and transport. Nickel's high affinity to sulfur- and phosphor-containing components such as DNA and proteins disrupts DNA replication and causes protein deformation [91].

References

1. Parente, D.M.; Cunha, C.; Mylonakis, E.; Timbrook, T.T. The Clinical Utility of Methicillin-Resistant Staphylococcus aureus (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis With Antimicrobial Stewardship Implications. Clin. Infect. Dis. 2018, 67, 1–7.
2. Wong, J.W.; Ip, M.; Tang, A.; Wei, V.W.; Wong, S.Y.; Riley, S.; Read, J.M.; Kwok, K.O. Prevalence and risk factors of community-associated methicillin-resistant Staphylococcus aureus carriage in Asia-Pacific region from 2000 to 2016: A systematic review and meta-analysis. Clin. Epidemiol. 2018, 10, 1489–1501.
3. Zarenezhad, E.; Mosslemin, M.H.; Alborzi, A.; Anaraki-Ardakani, H.; Shams, N.; Khoshnood, M.M.; Zarenezhad, A. Efficient synthesis of 3, 4-dihydro-1 H-quinoxalin-2-ones and 1 H-quinolin-2-ones and evaluation of their anti-bacterial activity. J. Chem. Res. 2014, 38, 337–340.
4. Vestergaard, M.; Frees, D.; Ingmer, H. Antibiotic Resistance and the MRSA Problem. Microbiol. Spectr. 2019, 7, 18.
5. Mlynarczyk-Bonikowska, B.; Kowalewski, C.; Krolak-Ulinska, A.; Marusza, W. Molecular Mechanisms of Drug Resistance in Staphylococcus aureus. Int. J. Mol. Sci. 2022, 23, 8088.
6. Liu, W.-T.; Chen, E.-Z.; Yang, L.; Peng, C.; Wang, Q.; Xu, Z.; Chen, D.-Q. Emerging resistance mechanisms for 4 types of common anti-MRSA antibiotics in Staphylococcus aureus: A comprehensive review. Microb. Pathog. 2021, 156, 104915.
7. Nandhini, P.; Kumar, P.; Mickymaray, S.; Alothaim, A.S.; Somasundaram, J.; Rajan, M. Recent Developments in Methicillin-Resistant Staphylococcus aureus (MRSA) Treatment: A Review. Antibiotics 2022, 11, 606.
8. Baede, V.O.; David, M.Z.; Andrasevic, A.T.; Blanc, D.S.; Borg, M.; Brennan, G.; Catry, B.; Chabaud, A.; Empel, J.; Enger, H.; et al. MRSA surveillance programmes worldwide: Moving towards a harmonised international approach. Int. J. Antimicrob. Agents 2022, 59, 106538.
9. Lee, A.S.; De Lencastre, H.; Garau, J.; Kluytmans, J.; Malhotra-Kumar, S.; Peschel, A.; Harbarth, S. Methicillin-resistant Staphylococcus aureus. Nat. Rev. Dis. Primers 2018, 4, 18033.
10. Schnitt, A.; Tenhagen, B.-A. Risk Factors for the Occurrence of Methicillin-Resistant Staphylococcus aureus in Dairy Herds: An Update. Foodborne Pathog. Dis. 2020, 17, 585–596.
11. Krukowski, H.; Bakuła, Z.; Iskra, M.; Olender, A.; Bis-Wencel, H.; Jagielski, T. The first outbreak of methicillin-resistant Staphylococcus aureus in dairy cattle in Poland with evidence of on-farm and intrahousehold transmission. J. Dairy Sci. 2020, 103, 10577–10584.
12. Schnitt, A.; Lienen, T.; Wichmann-Schauer, H.; Cuny, C.; Tenhagen, B.-A. The occurrence and distribution of livestock-associated methicillin-resistant Staphylococcus aureus ST398 on German dairy farms. J. Dairy Sci. 2020, 103, 11806–11819.
13. Turner, N.A.; Sharma-Kuinkel, B.K.; Maskarinec, S.A.; Eichenberger, E.M.; Shah, P.P.; Carugati, M.; Holland, T.L.; Fowler, V.G., Jr. Methicillin-resistant Staphylococcus aureus: An overview of basic and clinical research. Nat. Rev. Microbiol. 2019, 17, 203–218.
14. Hanberger, H.; Walther, S.; Leone, M.; Barie, P.S.; Rello, J.; Lipman, J.; Marshall, J.C.; Anzueto, A.; Sakr, Y.; Pickkers, P.; et al. Increased mortality associated with meticillin-resistant Staphylococcus aureus (MRSA) infection in the Intensive Care Unit: Results from the EPIC II study. Int. J. Antimicrob. Agents 2011, 38, 331–335.
15. Queck, S.Y.; Jameson-Lee, M.; Villaruz, A.E.; Bach, T.-H.L.; Khan, B.A.; Sturdevant, D.E.; Ricklefs, S.M.; Li, M.; Otto, M. RNAIII-Independent Target Gene Control by the agr Quorum-Sensing System: Insight into the Evolution of Virulence Regulation in Staphylococcus aureus. Mol. Cell 2008, 32, 150–158.
16. Mahdally, N.H.; George, R.F.; Kashef, M.T.; Al-Ghobashy, M.; Murad, F.E.; Attia, A.S. Staquorsin: A Novel Staphylococcus aureus Agr-Mediated Quorum Sensing Inhibitor Impairing Virulence in vivo Without Notable Resistance

Development. Front. Microbiol. 2021, 12, 700494.

17. Algammal, A.M.; Hetta, H.F.; Elkelish, A.; Alkhalifah, D.H.H.; Hozzein, W.N.; Batiha, G.E.-S.; El Nahhas, N.; Mabrok, M.A. Methicillin-Resistant Staphylococcus aureus (MRSA): One Health Perspective Approach to the Bacterium Epidemiology, Virulence Factors, Antibiotic-Resistance, and Zoonotic Impact. Infect. Drug Resist. 2020, 13, 3255–3265.
18. Cheung, G.Y.C.; Bae, J.S.; Liu, R.; Hunt, R.L.; Zheng, Y.; Otto, M. Bacterial virulence plays a crucial role in MRSA sepsis. PLoS Pathog. 2021, 17, e1009369.
19. Ghasemian, A.; Peerayeh, S.N.; Bakhshi, B.; Mirzaee, M. The Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs) Genes among Clinical Isolates of Staphylococcus aureus from Hospitalized Children. Iran. J. Pathol. 2015, 10, 258–264.
20. Ghasemian, A.; Peerayeh, S.N.; Bakhshi, B.; Mirzaee, M. Comparison of Biofilm Formation between Methicillin-Resistant and Methicillin-Susceptible Isolates of Staphylococcus aureus. Iran. Biomed. J. 2016, 20, 175–181.
21. Otto, M. MRSA virulence and spread. Cell. Microbiol. 2012, 14, 1513–1521.
22. Ahmad-Mansour, N.; Loubet, P.; Pouget, C.; Dunyach-Remy, C.; Sotto, A.; Lavigne, J.-P.; Molle, V. Staphylococcus aureus Toxins: An Update on Their Pathogenic Properties and Potential Treatments. Toxins 2021, 13, 677.
23. Kong, C.; Neoh, H.-M.; Nathan, S. Targeting Staphylococcus aureus Toxins: A Potential form of Anti-Virulence Therapy. Toxins 2016, 8, 72.
24. Salinas, N.; Colletier, J.-P.; Moshe, A.; Landau, M. Extreme amyloid polymorphism in Staphylococcus aureus virulent PSMα peptides. Nat. Commun. 2018, 9, 3512.
25. Bukowski, M.; Wladyka, B.; Dubin, G. Exfoliative toxins of Staphylococcus aureus. Toxins 2010, 2, 1148–1165.
26. Gaebler Vasconcelos, N.; de Lourdes Ribeiro de Souza da Cunha, M. Staphylococcal enterotoxins: Molecular aspects and detection methods. J. Public Health Epidemiol. 2010, 2, 29–42.
27. Weese, J.S. Methicillin-Resistant Staphylococcus aureus in Animals. ILAR J. 2010, 51, 233–244.
28. Graveland, H.; Wagenaar, J.A.; Bergs, K.; Heesterbeek, H.; Heederik, D. Persistence of Livestock Associated MRSA CC398 in Humans Is Dependent on Intensity of Animal Contact. PLoS ONE 2011, 6, e16830.
29. Dorado-García, A.; Bos, M.E.; Graveland, H.; Van Cleef, B.A.; Verstappen, K.M.; Kluytmans, J.A.; Wagenaar, J.A.; Heederik, D.J. Risk factors for persistence of livestock-associated MRSA and environmental exposure in veal calf farmers and their family members: An observational longitudinal study. BMJ Open 2013, 3, e003272.
30. Van Loo, I.; Huijsdens, X.; Tiemersma, E.; De Neeling, A.; van de Sande-Bruinsma, N.; Beaujean, D.; Voss, A.; Kluytmans, J. Emergence of methicillin-resistant Staphylococcus aureus of animal origin in humans. Emerg. Infect. Dis. 2007, 13, 1834.
31. van Duijkeren, E.; Moleman, M.; van Oldruitenborgh-Oosterbaan, M.S.; Multem, J.; Troelstra, A.; Fluit, A.; van Wamel, W.; Houwers, D.; de Neeling, A.; Wagenaar, J. Methicillin-resistant Staphylococcus aureus in horses and horse personnel: An investigation of several outbreaks. Veter. Microbiol. 2010, 141, 96–102.
32. Idelevich, E.A.; Lanckohr, C.; Horn, D.; Wieler, L.H.; Becker, K.; Koeck, R. Multidrug-resistant bacteria in Germany. The impact of sources outside healthcare facilities. Bundesgesundheitsblatt Gesundh. Gesundh. 2016, 59, 113–123.
33. Köck, R.; Ballhausen, B.; Bischoff, M.; Cuny, C.; Eckmanns, T.; Fetsch, A.; Harmsen, D.; Goerge, T.; Oberheitmann, B.; Schwarz, S.; et al. The impact of zoonotic MRSA colonization and infection in Germany. Berl. Munch. Tierarztl. Wochenschr. 2015, 127, 384–398.
34. Lienen, T.; Schnitt, A.; Hammerl, J.A.; Maurischat, S.; Tenhagen, B.-A. Genomic Distinctions of LA-MRSA ST398 on Dairy Farms From Different German Federal States With a Low Risk of Severe Human Infections. Front. Microbiol. 2021, 11, 575321.
35. Rybak, M.J.; Le, J.; Lodise, T.P.; Levine, D.P.; Bradley, J.S.; Liu, C.; Mueller, B.A.; Pai, M.P.; Wong-Beringer, A.; Rotschafer, J.C.; et al. Therapeutic Monitoring of Vancomycin for Serious Methicillin-resistant Staphylococcus aureus Infections: A Revised Consensus Guideline and Review by the American Society of Health-system Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Clin. Infect. Dis. 2020, 71, 1361–1364.
36. Washer, P.; Joffe, H. The “hospital superbug”: Social representations of MRSA. Soc. Sci. Med. 2006, 63, 2141–2152.
37. Chen, H.; Du, Y.; Xia, Q.; Li, Y.; Song, S.; Huang, X. Role of linezolid combination therapy for serious infections: Review of the current evidence. Eur. J. Clin. Microbiol. Infect. Dis. 2020, 39, 1043–1052.
38. Kelesidis, T.; Humphries, R.; Ward, K.; Lewinski, M.A.; Yang, O.O. Combination therapy with daptomycin, linezolid, and rifampin as treatment option for MRSA meningitis and bacteremia. Diagn. Microbiol. Infect. Dis. 2011, 71, 286–290.

39. Jacqueline, C.; Navas, D.; Batard, E.; Miegeville, A.-F.; Le Mabecque, V.; Kergueris, M.-F.; Bugnon, D.; Potel, G.; Caillon, J. In Vitro and In Vivo Synergistic Activities of Linezolid Combined with Subinhibitory Concentrations of Imipenem against Methicillin-Resistant Staphylococcus aureus. Antimicrob. Agents Chemother. 2005, 49, 45–51.

40. Mehta, S.; Singh, C.; Plata, K.B.; Chanda, P.K.; Paul, A.; Riosa, S.; Rosato, R.R.; Rosato, A.E. β-Lactams Increase the Antibacterial Activity of Daptomycin against Clinical Methicillin-Resistant Staphylococcus aureus Strains and Prevent Selection of Daptomycin-Resistant Derivatives. Antimicrob. Agents Chemother. 2012, 56, 6192–6200.

41. Alosaimy, S.; Sabagha, N.L.; Lagnf, A.M.; Zasowski, E.J.; Morrisette, T.; Jorgensen, S.C.J.; Trinh, T.D.; Mynatt, R.P.; Rybak, M.J. Monotherapy with Vancomycin or Daptomycin versus Combination Therapy with β-Lactams in the Treatment of Methicillin-Resistant Staphylococcus Aureus Bloodstream Infections: A Retrospective Cohort Analysis. Infect. Dis. Ther. 2020, 9, 325–339.

42. Dilworth, T.J.; Ibrahim, O.; Hall, P.; Sliwinski, J.; Walraven, C.; Mercier, R.-C. β-Lactams Enhance Vancomycin Activity against Methicillin-Resistant Staphylococcus aureus Bacteremia Compared to Vancomycin Alone. Antimicrob. Agents Chemother. 2014, 58, 102–109.

43. Morrisette, T.; Alosaimy, S.; Abdul-Mutakabbir, J.; Kebriaei, R.; Rybak, M. The Evolving Reduction of Vancomycin and Daptomycin Susceptibility in MRSA—Salvaging the Gold Standards with Combination Therapy. Antibiotics 2020, 9, 762.

44. Bellos, I.; Karageorgiou, V.; Pergialiotis, V.; Perrea, D. Acute kidney injury following the concurrent administration of antipseudomonal β-lactams and vancomycin: A network meta-analysis. Clin. Microbiol. Infect. 2020, 26, 696–705.

45. Tong, S.Y.; Lye, D.C.; Yahav, D.; Sud, A.; Robinson, J.O.; Nelson, J.; Archuleta, S.; Roberts, M.A.; Cass, A.; Davis, J. SEffect of vancomycin or daptomycin with vs without an antistaphylococcal β-lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia: A randomized clinical trial. JAMA 2020, 323, 527–537.

46. Wang, C.; Ye, C.; Liao, L.; Wang, Z.; Hu, Y.; Deng, C.; Liu, L. Adjuvant β-Lactam Therapy Combined with Vancomycin or Daptomycin for Methicillin-Resistant Staphylococcus aureus Bacteremia: A Systematic Review and Meta-analysis. Antimicrob. Agents Chemother. 2020, 64, e01377-20.

47. Mohamed, M.; Abdelkhalek, A.; Seleem, M. Evaluation of short synthetic antimicrobial peptides for treatment of drug-resistant and intracellular Staphylococcus aureus. Sci. Rep. 2016, 6, 29707.

48. Yao, C.-J.; Li, Y.-L.; Pu, M.-J.; Luo, L.-H.; Xiong, Q.; Xie, F.-J.; Li, T.-L.; Feng-Jiao, X. Aminoglycosides with Anti-MRSA Activity: A Concise Review. Curr. Top. Med. Chem. 2021, 21, 2483–2499.

49. Verma, R.; Verma, S.K.; Rakesh, K.P.; Girish, Y.R.; Ashrafizadeh, M.; Kumar, K.S.S.; Rangappa, K.S. Pyrazole-based analogs as potential antibacterial agents against methicillin-resistance staphylococcus aureus (MRSA) and its SAR elucidation. Eur. J. Med. Chem. 2021, 212, 113134.

50. Leng, B.; Yan, G.; Li, T.; Hou, N. Vancomycin-induced reversible pancytopenia and rash in a 16-month-old boy with osteomyelitis: A case report. Int. J. Clin. Pharmacol. Ther. 2020, 58, 242–246.

51. Niu, H.; Yang, T.; Wang, J.; Wang, R.; Cai, Y. Immunomodulatory Effect of Colistin and its Protective Role in Rats with Methicillin-Resistant Staphylococcus aureus-induced Pneumonia. Front. Pharmacol. 2021, 11, 602054.

52. Parish, D.; Scheinfeld, N. Ceftaroline fosamil, a cephalosporin derivative for the potential treatment of MRSA infection. Curr. Opin. Investig. Drugs 2008, 9, 201–209.

53. Shirley, D.-A.T.; Heil, E.L.; Johnson, J.K. Ceftaroline Fosamil: A Brief Clinical Review. Infect. Dis. Ther. 2013, 2, 95–110.

54. Torres, A.; Soriano, A.; Rivolo, S.; Remak, E.; Peral, C.; Kantecki, M.; Ansari, W.; Charbonneau, C.; Hammond, J.; Grau, S.; et al. Ceftaroline Fosamil for the Empiric Treatment of Hospitalized Adults with cSSTI: An Economic Analysis from the Perspective of the Spanish National Health System. Clin. Econ. Outcomes Res. 2022, 14, 149–161.

55. Stefani, S.; Bongiorno, D.; Mongelli, G.; Campanile, F. Linezolid Resistance in Staphylococci. Pharmaceuticals 2010, 3, 1988–2006.

56. Shariati, A.; Dadashi, M.; Chegini, Z.; van Belkum, A.; Mirzaii, M.; Khoramrooz, S.S.; Darban-Sarokhalil, D. The global prevalence of Daptomycin, Tigecycline, Quinupristin/Dalfopristin, and Linezolid-resistant Staphylococcus aureus and coagulase–negative staphylococci strains: A systematic review and meta-analysis. Antimicrob. Resist. Infect. Control. 2020, 9, 1–20.

57. Li, C.; Li, Z.; Gan, Y.; Jiang, F.; Zhao, H.; Tan, J.; Yang, Y.Y.; Yuan, P.; Ding, X. Selective Capture, Separation, and Photothermal Inactivation of Methicillin-Resistant Staphylococcus aureus (MRSA) Using Functional Magnetic Nanoparticles. ACS Appl. Mater. Interfaces 2022, 14, 20566–20575.

58. Mohamed, M.B.E.D.; El-Ela, F.I.A.; Mahmoud, R.K.; Farghali, A.A.; Gamil, S.; Aziz, S.A.A.A. Cefotax-magnetic nanoparticles as an alternative approach to control Methicillin-Resistant Staphylococcus aureus (MRSA) from different

sources. Sci. Rep. 2022, 12, 624.

59. Zhang, L.; Bhatti, M.M.; Michaelides, E.E.; Marin, M.; Ellahi, R. Hybrid nanofluid flow towards an elastic surface with tantalum and nickel nanoparticles, under the influence of an induced magnetic field. Eur. Phys. J. Spéc. Top. 2022, 231, 521–533.
60. Hou, Y.; Kondoh, H.; Ohta, T.; Gao, S. Size-controlled synthesis of nickel nanoparticles. Appl. Surf. Sci. 2005, 241, 218–222.
61. Abdollahi, A.; Mirzaei, E.; Amoozegar, F.; Moemenbellah-Fard, M.D.; Zarenezhad, E.; Osanloo, M. High Antibacterial Effect of Impregnated Nanofiber Mats with a Green Nanogel Against Major Human Pathogens. BioNanoScience 2021, 11, 549–558.
62. Qasemi, H.; Fereidouni, Z.; Karimi, J.; Abdollahi, A.; Zarenezhad, E.; Rasti, F.; Osanloo, M. Promising antibacterial effect of impregnated nanofiber mats with a green nanogel against clinical and standard strains of Pseudomonas aeruginosa and Staphylococcus aureus. J. Drug Deliv. Sci. Technol. 2021, 66, 102844.
63. Hulme, J. Application of Nanomaterials in the Prevention, Detection, and Treatment of Methicillin-Resistant Staphylococcus aureus (MRSA). Pharmaceutics 2022, 14, 805.
64. Nisar, P.; Ali, N.; Rahman, L.; Ali, M.; Shinwari, Z.K. Antimicrobial activities of biologically synthesized metal nanoparticles: An insight into the mechanism of action. JBIC J. Biol. Inorg. Chem. 2019, 24, 929–941.
65. Mendes, C.R.; Dilarri, G.; Forsan, C.F.; Sapata, V.d.M.R.; Lopes, P.R.M.; de Moraes, P.B.; Montagnolli, R.N.; Ferreira, H.; Bidoia, E.D. Antibacterial action and target mechanisms of zinc oxide nanoparticles against bacterial pathogens. Sci. Rep. 2022, 12, 2658.
66. Radzig, M.; Nadtochenko, V.; Koksharova, O.; Kiwi, J.; Lipasova, V.; Khmel, I. Antibacterial effects of silver nanoparticles on gram-negative bacteria: Influence on the growth and biofilms formation, mechanisms of action. Colloids Surf. B Biointerfaces 2013, 102, 300–306.
67. Nunez, N.V.A.; Villegas, H.H.L.; Turrent, L.D.C.I.; Padilla, C.R. Silver Nanoparticles Toxicity and Bactericidal Effect Against Methicillin-Resistant Staphylococcus aureus: Nanoscale Does Matter. Nanobiotechnology 2009, 5, 2–9.
68. Hemeg, H.A. Nanomaterials for alternative antibacterial therapy. Int. J. Nanomed. 2017, 12, 8211–8225.
69. Gwon, K.; Kim, Y.; Cho, H.; Lee, S.; Yang, S.-H.; Kim, S.-J.; Lee, D. Robust Copper Metal–Organic Framework-Embedded Polysiloxanes for Biomedical Applications: Its Antibacterial Effects on MRSA and In Vitro Cytotoxicity. Nanomaterials 2021, 11, 719.
70. Kadiyala, U.; Turali-Emre, E.S.; Bahng, J.H.; Kotov, N.A.; VanEpps, J.S. Unexpected insights into antibacterial activity of zinc oxide nanoparticles against methicillin resistant Staphylococcus aureus (MRSA). Nanoscale 2018, 10, 4927–4939.
71. Ahmad, A.; Sabir, A.; Iqbal, S.S.; Felemban, B.F.; Riaz, T.; Bahadar, A.; Hossain, N.; Khan, R.U.; Inam, F. Novel antibacterial polyurethane and cellulose acetate mixed matrix membrane modified with functionalized TiO2 nanoparticles for water treatment applications. Chemosphere 2022, 301, 134711.
72. Javed, R.; Ain, N.U.; Gul, A.; Ahmad, M.A.; Guo, W.; Ao, Q.; Tian, S. Diverse biotechnological applications of multifunctional titanium dioxide nanoparticles: An up-to-date review. IET Nanobiotechnol. 2022, 16, 171–189.
73. Abebe, B.; Zereffa, E.A.; Tadesse, A.; Murthy, H.C.A. A Review on Enhancing the Antibacterial Activity of ZnO: Mechanisms and Microscopic Investigation. Nanoscale Res. Lett. 2020, 15, 190.
74. Al-Shawi, S.G.; Andreevna Alekhina, N.; Aravindhan, S.; Thangavelu, L.; Elena, A.; Viktorovna Kartamysheva, N.; Rafkatovna Zakieva, R. Synthesis of NiO nanoparticles and sulfur, and nitrogen co doped-graphene quantum dots/nio nanocomposites for antibacterial application. J. Nanostruct. 2021, 11, 181–188.
75. Kannan, K.; Radhika, D.; Nesaraj, A.; Sadasivuni, K.K.; Reddy, K.R.; Kasai, D.; Raghu, A.V. Photocatalytic, antibacterial and electrochemical properties of novel rare earth metal oxides-based nanohybrids. Mater. Sci. Energy Technol. 2020, 3, 853–861.
76. Munawar, T.; Iqbal, F.; Yasmeen, S.; Mahmood, K.; Hussain, A. Multi metal oxide NiO-CdO-ZnO nanocomposite–synthesis, structural, optical, electrical properties and enhanced sunlight driven photocatalytic activity. Ceram. Int. 2020, 46, 2421–2437.
77. Esmaeili, F.; Hosseini-Nasr, M.; Rad-Malekshahi, M.; Samadi, N.; Atyabi, F.; Dinarvand, R. Preparation and antibacterial activity evaluation of rifampicin-loaded poly lactide-co-glycolide nanoparticles. Nanomed. Nanotechnol. Biol. Med. 2007, 3, 161–167.
78. Jiang, J.-L.; Li, Y.-F.; Fang, T.-L.; Zhou, J.; Li, X.-L.; Wang, Y.-C.; Dong, J. Vancomycin-loaded nano-hydroxyapatite pellets to treat MRSA-induced chronic osteomyelitis with bone defect in rabbits. Inflamm. Res. 2011, 61, 207–215.

79. Saadh, M. Effect of silver nanoparticles on the antibacterial activity of Levofloxacin against methicillin-resistant Staphylococcus aureus. Eur. Rev. Med. Pharmacol. Sci. 2021, 25, 5507–5510.
80. Wang, G.; Wang, J.-J.; Li, F.; To, S.-S.T. Development and Evaluation of a Novel Drug Delivery: Pluronics/SDS Mixed Micelle Loaded With Myricetin In Vitro and In Vivo. J. Pharm. Sci. 2016, 105, 1535–1543.
81. Jones, S.; Pramanik, A.; Kanchanapally, R.; Nellore, B.P.V.; Begum, S.; Sweet, C.; Ray, P.C. Multifunctional Three-Dimensional Chitosan/Gold Nanoparticle/Graphene Oxide Architecture for Separation, Label-Free SERS Identification of Pharmaceutical Contaminants, and Effective Killing of Superbugs. ACS Sustain. Chem. Eng. 2017, 5, 7175–7187.
82. Devlin, H.; Fulaz, S.; Hiebner, D.W.; O'Gara, J.P.; Casey, E. Enzyme-Functionalized Mesoporous Silica Nanoparticles to Target Staphylococcus aureus and Disperse Biofilms. Int. J. Nanomed. 2021, 16, 1929–1942.
83. Wang, Z.K.; Kuok, M.H.; Ng, S.C.; Lockwood, D.J.; Cottam, M.G.; Nielsch, K.; Wehrspohn, R.B.; Gösele, U. Spin-Wave Quantization in Ferromagnetic Nickel Nanowires. Phys. Rev. Lett. 2002, 89, 027201.
84. Zheng, W.; Sun, C.Q. Electronic process of nitriding: Mechanism and applications. Prog. Solid State Chem. 2006, 34, 1–20.
85. Lee, K.-B.; Park, S.; Mirkin, C.A. Multicomponent Magnetic Nanorods for Biomolecular Separations. Angew. Chem. Int. Ed. 2004, 43, 3048–3050.
86. Hatamifard, A.; Nasrollahzadeh, M.; Sajadi, S.M. Biosynthesis, characterization and catalytic activity of an Ag/zeolite nanocomposite for base- and ligand-free oxidative hydroxylation of phenylboronic acid and reduction of a variety of dyes at room temperature. New J. Chem. 2016, 40, 2501–2513.
87. Jaji, N.-D.; Lee, H.L.; Hussin, M.H.; Akil, H.; Zakaria, M.R.; Othman, M.B.H. Advanced nickel nanoparticles technology: From synthesis to applications. Nanotechnol. Rev. 2020, 9, 1456–1480.
88. Iqbal, J.; Abbasi, B.A.; Mahmood, T.; Hameed, S.; Munir, A.; Kanwal, S. Green synthesis and characterizations of Nickel oxide nanoparticles using leaf extract of Rhamnus virgata and their potential biological applications. Appl. Organomet. Chem. 2019, 33, e4950.
89. Galdiero, S.; Falanga, A.; Berisio, R.; Grieco, P.; Morelli, G.; Galdiero, M. Antimicrobial Peptides as an Opportunity Against Bacterial Diseases. Curr. Med. Chem. 2015, 22, 1665–1677.
90. Xing, K.; Zhu, X.; Peng, X.; Qin, S. Chitosan antimicrobial and eliciting properties for pest control in agriculture: A review. Agron. Sustain. Dev. 2015, 35, 569–588.
91. Chaudhary, R.G.; Tanna, J.A.; Gandhare, N.V.; Rai, A.R.; Juneja, H.D. Synthesis Of Nickel Nanoparticles: Microscopic Investigation, An Efficient Catalyst And Effective Antibacterial Activity. Adv. Mater. Lett. 2015, 6, 990–998.