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Mini-Review

2D and Heterostructure Nanomaterial Based Strategies for Combating Drug-Resistant Bacteria

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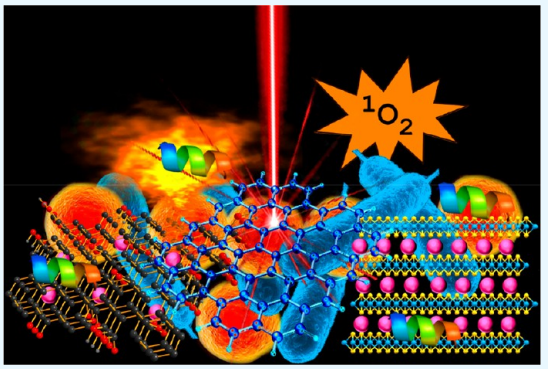
ABSTRACT: In the last three decades, there has been a huge increase in the number of antibiotic-resistant bacterial strains, which is becoming a serious threat to public health. Since the discovery of new effective antibiotics has dramatically decreased in last ten years, there are huge initiatives to develop new antimicrobial approaches to fight drug-resistant bacterial infections. In the last decade, a new nanoparticle-based tool has emerged to combat deadly bacterial infections, which may overcome the barriers faced by antibiotic resistance. The current mini-review highlights recent reports on two-dimensional (2D) graphene oxide (GO), 2D transition metal dichalcogenides (TMD), 2D MXenes, and 2D heterostructure material-based approaches to tackle bacteria. Notably, we discuss the major design criteria which have been used to develop novel antimicrobial 2D and heterostructure materials to eliminate bacterial infections. Next, details on the various mechanisms underlying antibacterial activity for 2D and heterostructure materials such as physical/mechanical damage, lipid extraction, oxidative stress, and photothermal/photodynamic effects have been discussed. Finally, we highlight the promises, major challenges, and prospects of nanomaterial-based approaches to combat multidrug-resistant bacterial infections.



INTRODUCTION

The discovery of penicillin antibiotics by Dr. Alexander Fleming in 1928[1] revolutionized the medical treatment for infectious diseases. The success of penicillin encouraged scientists to discover different types of antibiotics such as cephalosporins, aminoglycosides, glycopeptides, and quinolones.[2−6] It is now well documented that antibiotics kill bacteria by targeting essential survival processes.[5−9] As reported by several groups, antibiotics have the ability to inhibit cell wall synthesis which interferes with the bacterial reproduction.[3−9] Similarly, antibiotics have the capability to block the synthesis of vital proteins, DNA and RNA. As a result, it suspends the growth of bacteria.[4−9] Unfortunately, in the last few decades bacteria have acquired resistance to antibiotics available in the market, and as a result, infections caused by drug-resistant bacteria cannot be treated easily.[5−9]

There are several possible mechanisms through which bacteria become drug resistant, and these are increased efflux due to overexpression of efflux pumps, enzyme inactivation, decreased cell permeability, target protection, altered target site/enzyme, etc.[2,4−9] For example, it is now well documented that carbapenem-resistant Enterobacteriaceae *Escherichia coli* (*CRE-E. coli*), Gram-negative bacteria, has the capability to restrict the entry of antibiotics into the outer membrane.[4−9] *CRE-E. coli* is capable of changing the nature of the cell wall, leading to antibiotics becoming ineffective and the bacteria becoming resistant to most available antibiotics in the market.[5−9] Recent reports indicate that the "super-resistant" gene New Delhi metallo-beta-lactamase **1** (NDM-1), which exists in multidrug-resistant (MDR) bacteria, has the capability to cause enzymatic degradation of β-lactam antibiotics.[4−9] As a result, these bacteria became resistant to a broad range of antibiotics.[5−9] For example, Gram-positive bacteria such as *Klebsiella pneumoniae* have the ability to produce extended-spectrum beta-lactamases (ESBL), which allow *Klebsiella pneumoniae* to be resistant to virtually all beta-lactam antibiotics.[4−9]

In the last two decades, the development of new types of antibiotics has been declining rapidly, leaving no options to treat resistant bacteria.[2,4−9] As a result, infectious disease treatment has been challenged by bacteria, which are responsible for more than a million deaths in this world every year.[4−9] As per the world health organization (WHO),[3] if we cannot find an

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alternative way to tackle bacteria, by 2050 drug-resistant bacteria could kill 10 million people/year which is more than the number of people dying from cancer now. All the above facts have triggered initiatives in this world for the development of novel antimicrobial compounds for targeted killing of bacteria.[10−20] In the last 25 years, one of the very highly promising approaches to combating bacteria is nanomaterial=based antibacterial agents.[4−30] We and other groups have demonstrated that zero-dimensional (0D) to two-dimensional (2D) nanomaterial-based approaches can be highly promising alternatives for bacteria treatment.[10−35] 0D plasmonic nanoparticles such as silver nanoparticles have been demonstrated to exhibit high antibacterial activity toward drug-resistant bacteria.[8−20] It is now well documented that nanoparticles combat bacteria via several different mechanisms,[4−15] as shown in Figure 1.

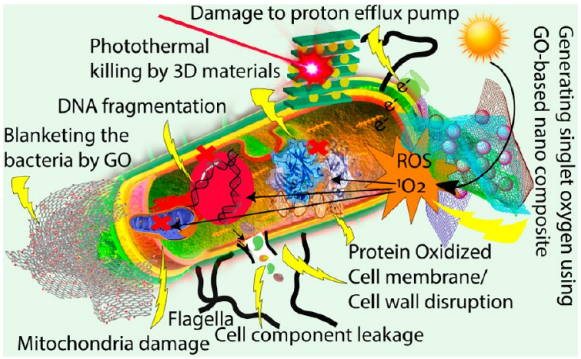

Figure 1. Scheme showing a possible bacteria-combating mechanism of different nanomaterials via bacterial cell damage, cell component leakage, photodynamic (PDT) killing via ROS, and photothermal (PTT) killing via disruption of genomic DNA, proteins, and cellular metabolism.

Nanoparticles have the capability to physically damage the cell membrane.[4−20] They can also generate reactive oxygen species (ROS) and free radicals.[21−35] The above process increases the oxidative stress, which enhances the fragmentation of genomic DNA and damages the cellular structural integrity.[20−35] It is now well documented that nanoparticles exhibit high membrane permeability in comparison to antibiotics.[4−15] Recent reports also indicate that nanoparticle-based antimicrobial agents have good capacity to act as efflux pump inhibitors.[4−20] Due to the above facts, nanomaterial-based antimicrobial agents are less prone to induce bacterial resistance in comparison to antibiotics available now in the market.[20−35] As a result, scientists have great hope that nanomaterial-based antibacterial agents will provide a new way to treat antibacterial infections.[4−20]

In the last two decades, many different families of nanomaterials including 0D metal nanoparticles, semiconductor nanodots, and carbon dots (one-dimensional (1D) nanorods, carbon nanotubes, 2D graphene oxide (GO), 2D transition metal dichalcogenides (TMD), and heterostructure materials) have been developed to combat bacterial infection.[4−35] In the last decade, we and others have published several review articles based on 0D and 1D nanomaterial-based antibacterial agents.[4−10] In this current mini-review, we have highlighted 2D-GO, TMD, MXene, and heterostructure material-based approaches to tackle bacteria.[4−35] Here we have discussed the major design criteria which has been used to develop novel antimicrobial nanotherapeutics and various mechanisms of antibacterial action which have been used to eliminate drug-resistant bacterial infections. Lastly, we have highlighted the possible challenges in using 2D GO, TMD, and 2D−0D heterostructure material-based approaches in practical applications for combating bacteria.

Combating Bacteria Using 2D-GO- and GO-Based Heterostructures. After the first observation in 2010 by Hu et al.[13] that graphene oxide (GO) and reduced graphene oxide (rGO) can be used as antibacterial materials, interest has rapidly grown to develop GO-based material for combating bacteria.[11−25] GO-containing sp^2 carbons and oxygen-containing functional groups such as carboxy, hydroxy, and epoxy allow high dispersion in aqueous medium.[11−25] Due to the ease of synthesis in a large scale, tunable size-dependent properties, low cytotoxicity, and high biocompatibility, in the last several years our group and other groups have been developing GO-based material for biological antimicrobial agents.[11−25] As reported by several groups, the antibacterial mechanism of GO involves both physical and chemical modes of action[11−25] as shown in Figure 2A. We and others have shown that chemical modes of action occur via ROS generation or through direct electron transfer.[11−25] On the other hand, several reported experimental data indicate that physical modes of action occur via direct contact with GO followed by penetration of the cell membrane.[11−25]

Liu et al.[15] compared *Escherichia coli* (*E. coli*) bacteria combating capability by GO and reduced graphene oxide (rGO) with graphite (Gt) and graphite oxide (GtO) as shown in Figures 2B−2E. Their reported data[15] show low antibacterial activity for graphite and graphite oxide, which is mostly due to lower dispersion stabilities. Their reported data indicate that the antibacterial performance for GO is ∼69.3% which is much higher than that of rGO, which is ∼45.9%.[15] Scanning electron microscopy (SEM) data as shown in Figures 2C−2D indicate that GO-exposed *E. coli* are almost evenly wrapped by GO layers.[15] On the other hand, rGO aggregates trap *E. coli*. Liu et al.[15] have argued that after wrapping the sharp edge of graphene nanosheets has the capability for significant membrane stress,[15] where GO layers are acting as "cutters" to damage cell membranes. Experimental data reported by Liu et al.[15] demonstrated that small-sized GO containing a high density of oxygen-containing functional groups will wrap the bacterial cells, which will induce membrane stress leading to cell death.[15]

Similarly, experimental data from other groups[15−24] also indicate that direct contact between Gram-positive and Gram-negative bacteria with graphene nanosheets could result in loss of bacterial membrane integrity and leakage of RNA/DNA. Zhao et al.[24] have reported the possible antimicrobial mechanism associated with aerobic reduction of GO as shown in Figures 2F and 2G. Their reported data[24] demonstrated that GO interacts with membrane-bound cytochrome *c* of *E. coli*. Zhao et al.[24] have indicated that the above interaction helps for shuttling electrons from the respiratory chain to extracellular molecular oxygen. As a result, superoxide anions ($O_2^{\bullet-}$) form, which in turn reduces GO.[24] Zhao et al.[24] showed that the reduction process interrupts the respiration chain and enhances the antimicrobial activity. From the experimental results, Zhao et al.[24] concluded that GO can serve as a conductive bridge to shuttle electrons from the intracellular respiratory chain to extracellular molecular oxygen. It also promotes $O_2^{\bullet-}$ production, which in turn reduced GO. The above process severed oxidative damage of bacteria.[24] Liu et al.[20] have reported lateral size-dependent antibacterial activities of GO sheets toward *E. coli* bacteria. As shown in Figures 3A−C, their reported data indicate that larger GO sheets exhibit stronger

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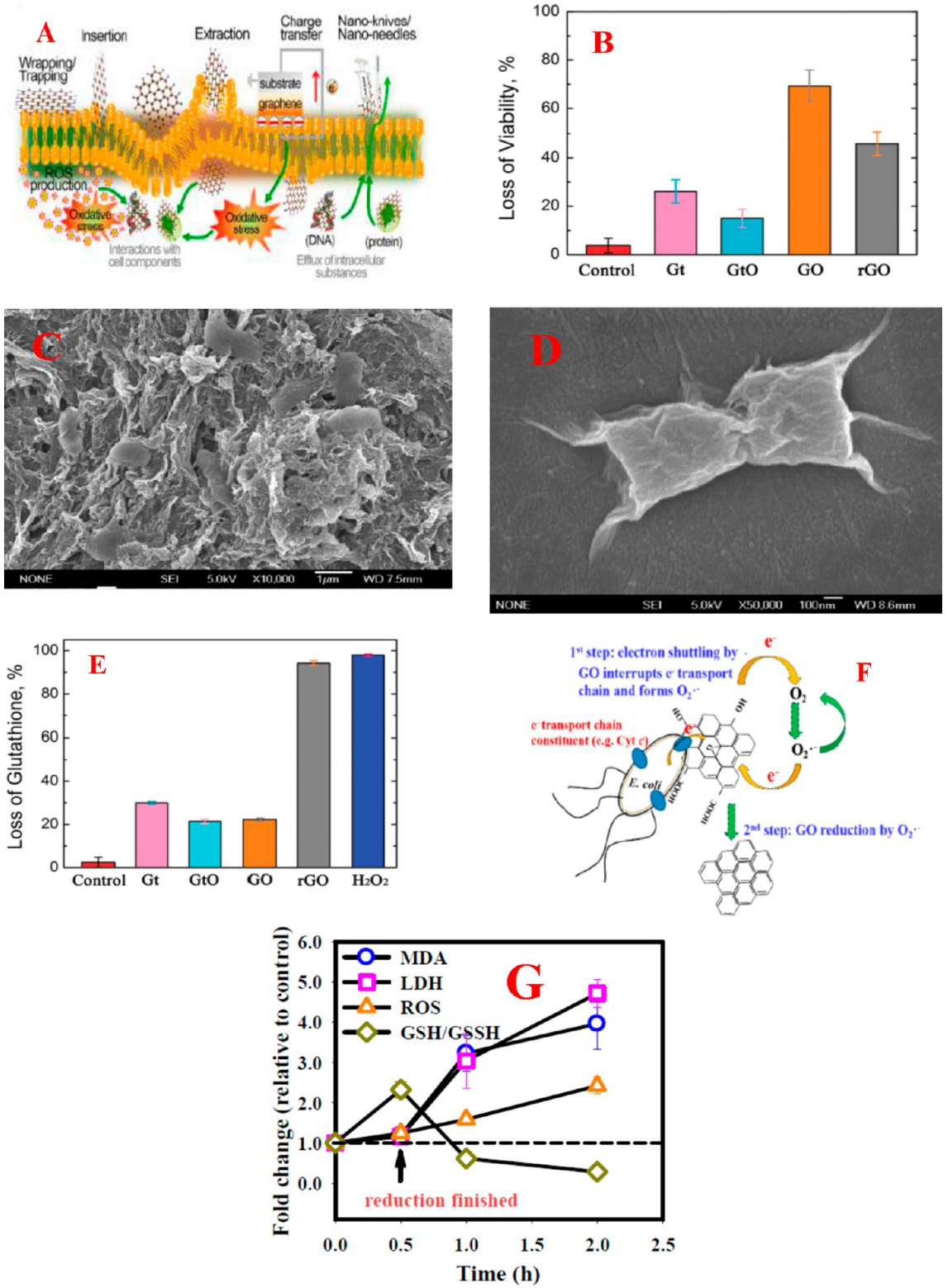

Figure 2. (A) Summaries of graphene-related antimicrobial mechanisms (adapted with permission from ref 14. Copyright 2016, American Chemical Society). (B) Cell viability for *E. coli* using Gt, GtO, GO, and rGO dispersions. (C) SEM image of *E. coli* cells after incubation with rGO dispersion (40 μg/mL) for 2 h. (D) SEM image of *E. coli* cells after incubation with GO dispersion (40 μg/mL) for 2 h. (E) Oxidation of glutathione by graphene-based materials, which shows loss of GSH after in vitro incubation with 40 μg/mL of Gt, GtO, GO, and rGO dispersions for 2 h. H_2O_2 (1 mM) is a positive control (adapted with permission from ref 15. Copyright 2011, American Chemical Society). (F) Bioreduction mechanism using GO as an antibacterial agent for *E. coli*. (G) Changes of malondialdehyde (MDA), lactase dehydrogenase (LDH), reactive oxygen species (ROS) content, and glutathione/oxidized glutathione (GSH/GSSH) ratio over time (adapted with permission from ref 24. Copyright 2018, American Chemical Society).

antibacterial activity than smaller ones. Experimental results using atomic force microscopy (AFM) analysis indicate GO sheets interact strongly with cells as shown in Figures 3A,B.[20] From AFM data, Liu et al.[20] have argued that large GO sheets

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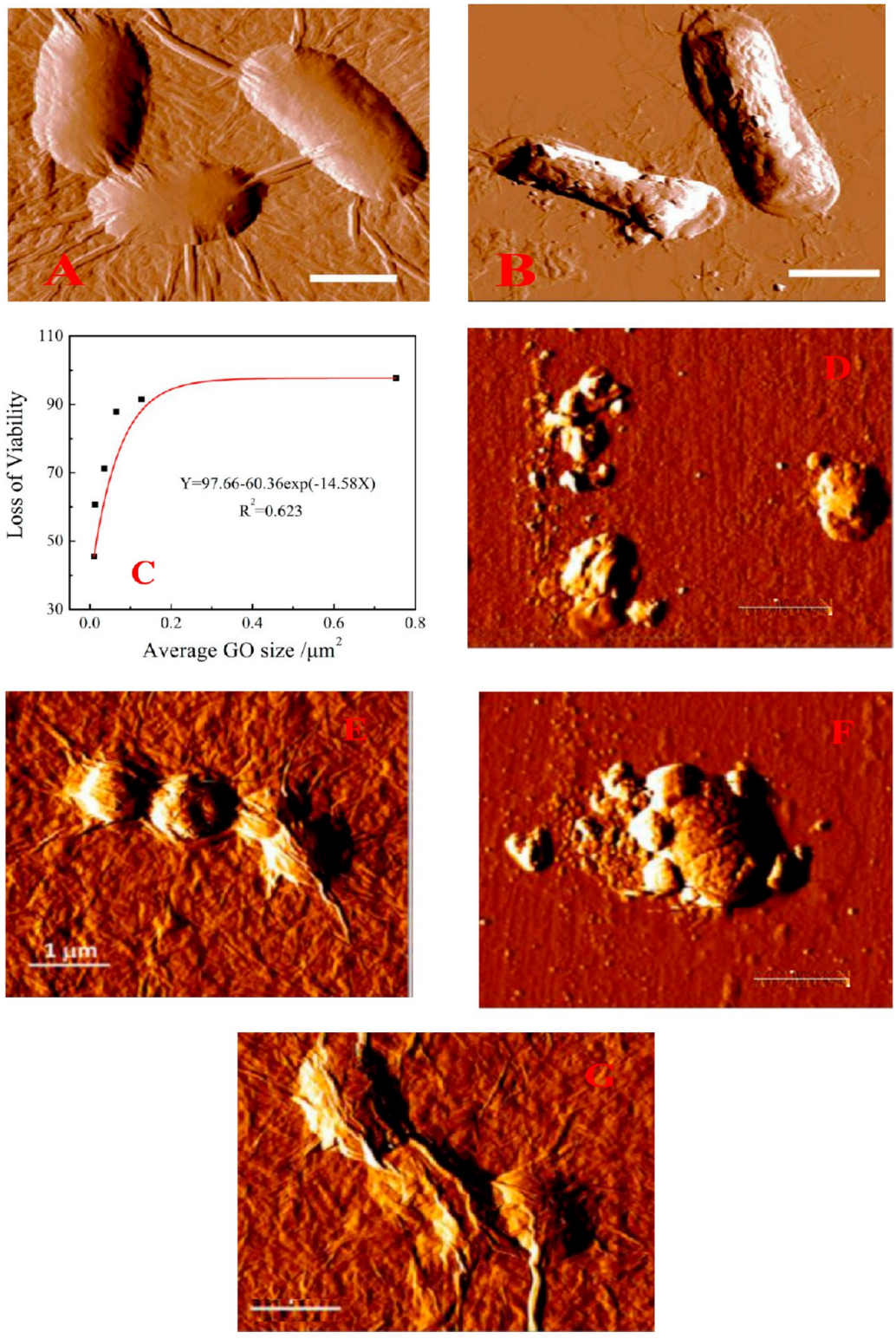

Figure 3. AFM amplitude and 3D images of *E. coli* cells after incubation with GO sheets. (A) *E. coli* incubation with the 40 μg/mL GO-0 (GO sheet with average size of 0.753 μm^2 was prepared originally before sonication) suspension for 2 h and (B) *E. coli* after incubation with the 40 μg/mL GO-240 (GO sheet with average size of 0.010 μm^2 was prepared by sonication for 240 min) suspension for 2 h. The scale bars are 1 μm. (C) Correlation between the loss of *E. coli* cell viability and the average size of GO sheets (adapted with permission from ref 20. Copyright 2012, American Chemical Society). (D) AFM image of *S. aureus* at low GO concentration. (E) AFM image of *S. aureus* at high GO concentration in the presence of salts. (F) AFM image of *E. coli* at low GO concentration. (G) AFM image of *E. coli* at high GO concentration in the presence of salts. The scale bars are 1 μm (adapted with permission from ref 22. Copyright 2017, American Chemical Society).

more easily cover cells. As a result, cells cannot proliferate once fully covered, resulting in the cell viability loss.

On the other hand, small GO can adhere to the bacterial surfaces, which allow weaker antibacterial activity.[20] Due to the

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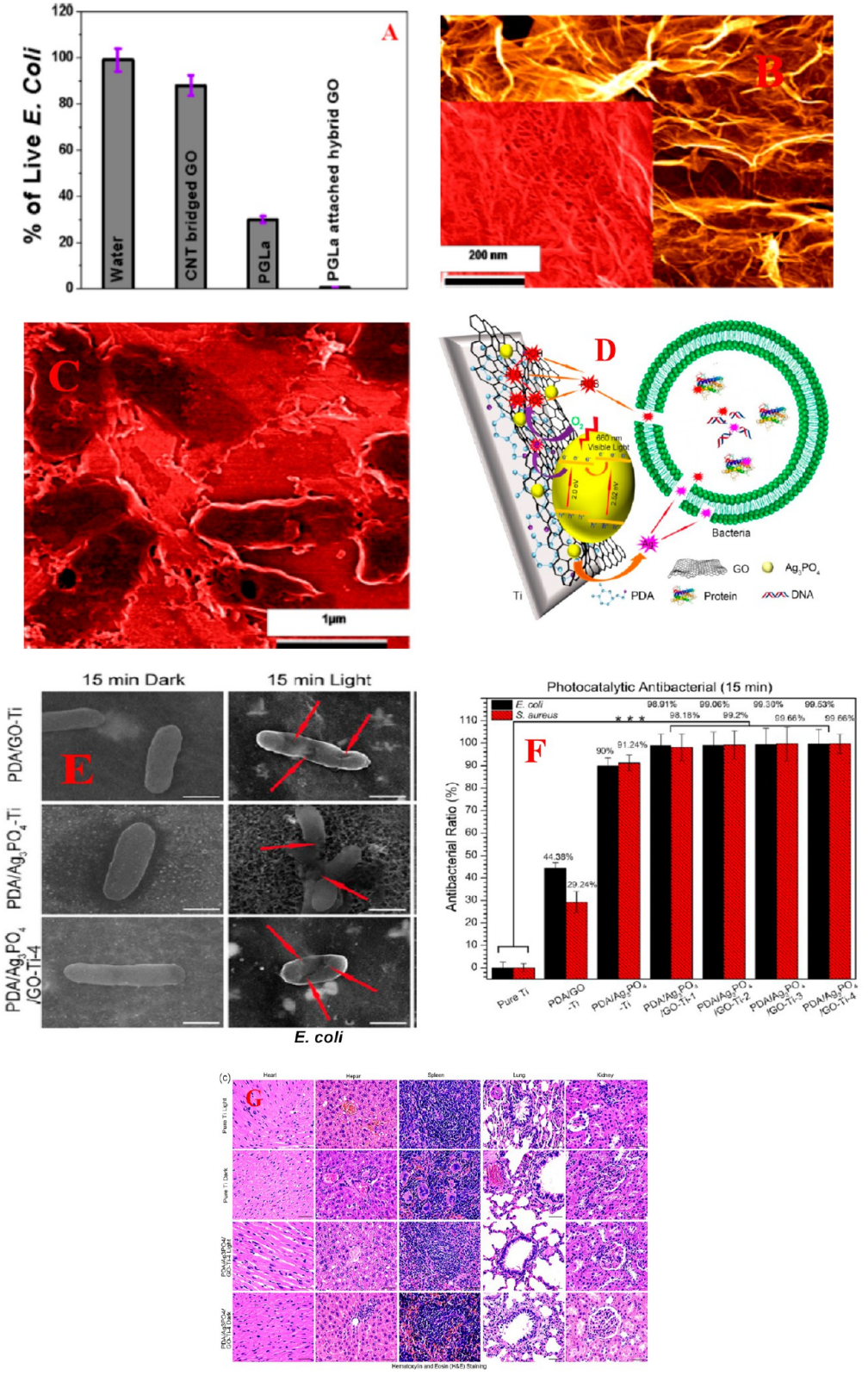

Figure 4. (A) Reverse transcription polymerase chain reaction (RTPCR) data that show *E. coli* O157:H7 killing efficiency using CNT-bridged 3D GO without the PGLa peptide, with only the PGLa peptide, and with the PGLa peptide-conjugated CNT-bridged 3D graphene oxide membrane. (B) SEM image of PGLa and glutathione-conjugated CNT-bridged graphene oxide membrane. (C) SEM image demonstrating the capture of *E. coli* O157:H7 by PGLa-conjugated CNT-bridged 3D graphene oxide-based membrane (adapted with permission from ref 12. Copyright 2015, American Chemical Society). (D) Schematic illustration shows the synergistic bacteria-killing behavior using the PDA/Ag_3PO_4/GO hybrid. (E) Surface morphology of the bacteria on the sample surface after culturing for 15 min in darkness versus irradiation for 15 min with 660 nm visible light. The scale bars are 1 μm. (F) Antibacterial property analysis after exposure to 660 nm visible light for 15 min. (G) H&E staining of visceral tissue slices of rats after implantation for 3 days (adapted with permission from ref 23. Copyright 2018, American Chemical Society).

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penetration of the cell membrane by 2D GO, loss of membrane integrity may happen via pore formation or extraction of lipid molecules. Palmieri et al.[22] reported how GO concentration and the surrounding media can manipulate the antimicrobial property. As shown in Figure 3D−G, their experimental data show that at low GO concentration GO cuts microorganism membranes for *S. aureus* and *E. coli*. Palmieri et al.[22] have demonstrated that when the concentration is below 6 μg/mL GO acts as a knife that cuts bacterial membranes. On the other hand, as GO concentration increases, the GO killing efficacy increases only in water.[22] Their experimental observation, as shown in Figure 3D−G, indicates that in other solutions, due to the aggregation which shields GO edges, there is no impact on microbial growth. Their reported experimental data show that when the concentration is higher than 100 μg/mL GO cluster size becomes much larger than bacteria.[22] As a result, GO aggregates wrap bacteria and impede their growth. Their studies clearly show that GO versatility can be exploited for the treatments against multidrug- resistant bacteria.

Several reports in the last decade indicate that other than membrane stress mediated via wrapping oxidative stress produced by GO and rGO also can be the cause of cell death.[10−24] It is now well documented that oxidative stress can interfere with bacterial metabolism.[10−20] Oxidative stress induced by nanomaterials also has the capability to disrupt essential cellular functions, which can lead to cell death.[14−24] Oxidative stress usually occurs via two different pathways. The first one is ROS-dependent, and the second one is the ROS-independent pathway.[10−20] Liu et al.[15] have performed *in vitro* GSH oxidation test experiments as shown in Figure 2E. Their reported data clearly indicate that rGOs and Gt are capable of inducing superoxide anion-independent oxidative stress on bacterial cells. On the other hand, GO has the lowest GSH oxidation capacities with respect to GT, GTO, and rGO. From all the experimental data, Liu et al.[15] have concluded that graphene-based destruction of bacteria can be attributed to both membrane damage and oxidative stress.

It is now well documented that lipid peroxidation, which is also known as ROS-mediated oxidation of lipid molecules, is a very important oxidative pathway to kill bacteria.[10−24] Krishnamoorthy et al.[17] have reported that graphene nanosheets enhanced the ultrasound-induced lipid peroxidation. Their reported data show that with respect to the control group lipid peroxidation increased by 117% and 109% after exposure to 10 and 5 μg/mL of graphene. Zucker et al.[19] reported the disruption of phospholipid vesicles due to 2D GO and cell interactions. Their dye leakage experiment shows that the extent of membrane integrity loss was dependent on total surface area and not edge length.[19] In the past decade, heterostructure building blocks using 2D GO, 1D, and 0D materials have opened unique opportunities to be studied for use as antibacterial material due to the combined advantages of the individual material.[10−20] As we have discussed, although GO is able to kill bacteria, the killing efficiency is less than 50%. To improve the killing efficiency to 100%, several heterostructure-based materials have been designed recently and reported to have the capability for 100% killing of bacteria.[10−20] We have reported[12] that the PGLa peptide (Gly-Met-Ala-Ser-Lys-Ala-Gly-Ala-Ile-Ala-Gly-Lys-Ile-Ala-Lys-Val-Ala-Leu-Lys-Ala-Leu-NH_2) conjugated CNT-bridged graphene oxide membrane can be used for disinfection of pathogenic *E. coli* O157:H7 bacteria.

For the design of heterostructure-based antibacterial material, as shown in Figures 4A−4C, we have used 1D CNTs to physically separate 2D graphene oxide sheets from aggregation.[12] To increase the percentage of killing efficiency, we have developed PGLa antimicrobial peptide which has the capability to kill *E. coli* O157:H7 on contact by interacting with their lipid membranes.[12] As shown in Figures 4A−4C, our experimental disinfection data show that the PGLa peptide can kill roughly 70% of *E. coli* O157:H7 bacteria in the absence of CNT-bridged 3D graphene oxide.[12] On the other hand, CNT-bridged 3D graphene can kill only 11% *E. coli* O157:H7 bacteria without PGLa.[12] Our reported data clearly show that PGLa-attached CNT-bridged 3D graphene oxides are able to kill 100% of *E. coli* O157:H7 bacteria.[12] We have concluded that CNT-bridged 3D graphene oxide helps to trap *E. coli*, and this situation allows PGLa to bind and penetrate the outer membrane of bacteria and kill *E. coli* O157:H7 bacteria.[12]

Xie et al. reported[23] the design of hybrid polydopamine (PDA)/Ag_3PO4/GO-based antibacterial material to achieve rapid bacteria killing and eliminate biofilms in situ. As shown in Figure 4D−4G, in their design they have explored the synergistic actions of Ag^+ and ROS produced by Ag_3PO_4 under irradiation of 660 nm visible light.[23] For this purpose, they have tuned the bandgap of the Ag_3PO_4 NPs using GO. The observed that the synergistic killing mechanism is due to an increase in the membrane permeability by ROS, which enables Ag^+ to enter the bacteria more easily.[23] As a result, both Ag^+ and ROS can destroy the DNA and proteins synergistically. Their reported experimental data indicate that the antimicrobial properties for the hybrid vary with the composition of particles.[23] They have argued that due to the larger specific surface area for the heterostructure it leads to more effective release of Ag^+ and absorption of more photons to produce ROS.[23] As shown in Figure 4G, the histological section by immunohistochemical staining of neutrophils and lymphocytes shows excellent photocatalytic antibacterial activity. Feng et al.[25] reported a reduced graphene oxide/Au nanostar (rGO/AuNS) heterostructure based highly effective photothermal agent, which has the capability to enhance the photothermal conversion in comparison to the pure rGO nanosheets and AuNS. Their reported data show that the rGO/AuNS exhibits promising intrinsic antibacterial activity for MRSA. Very recently, we have reported[11] the design of a polydopamine nanoparticle (PDNP) attached GO-conjugated ε-poly-L-lysine (ε-PL) antimicrobial peptide based novel heterostructure, which can be used for disinfection of drug-resistant pathogens from environmental samples. Reported data show that[11] a PDNP-attached GO-conjugated ε-poly-L-lysine (ε-PL) based heterostructure can be used for capturing 100% bacteria. Experimental drug-resistant bacteria killing data[11] demonstrated that the heterostructure has the capability to eradicate different drug-resistant bacteria such as β-lactamase (ESBL)-producing *Klebsiella pneumoniae* (KPN) and methicillin-resistant *Staphylococcus aureus* (MRSA). Shoeb et al.[21] have reported a graphene/polyindole (Gr@PIn) heterostructure-based antibacterial nanocomposite for the treatment of MRSA skin infection in BALB/c mice. Their reported experimental results[21] show that Gr@PIn nanocomposites are highly effective in inhibiting MRSA.

Their experimental data[21] with BALB/c mice, as shown in Figure 5A−5D, show that the graphene-based heterostructure has great potential to prevent bacterial infection under in vivo environments using an *S. aureus*-mediated skin contagion in BALB/c mice. Reported data[21] indicate that right after the treatment using Gr@PIn nanocomposites the skin attained a typical architecture. Shoeb et al.[21] have shown that the Gr@PIn

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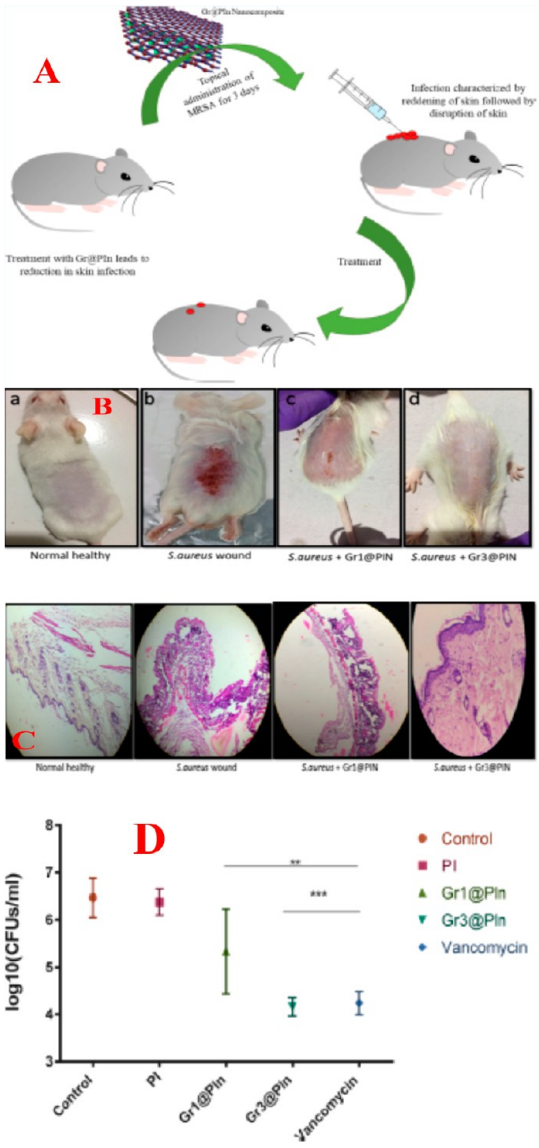

Figure 5. (A) Schematic representation shows a graphene/polyindole-based nanocomposite for the treatment of MRSA skin infection in BALB/c mice (adapted with permission from ref 21. Copyright 2018, American Chemical Society). (B) Efficacy against the examination of mice skin. (C) On day 11, biopsy specimens were taken instantly and stained using hematoxylin and eosin (HE) staining. (D) After treatment with various Gr@PIn, skin lesions were cut; the homogenized and bacterial count was determined by CFU assay (adapted with permission from ref 21. Copyright 2018, American Chemical Society).

nanocomposite can potentially damage the cell wall of MRSA and successfully inhibit the biofilm formation.

In this section, we have discussed 2D-GO and hetero-structure-based design of antibacterial strategy for killing bacteria. The reported antibacterial mechanism of GO involves wrapping of the bacteria membrane. However, the detailed understanding on why the wrapped bacteria are killed is lacking. As a result, detailed studies need to be conducted to find the actual mechanism behind the wrapping-based bacteria killing which depends on the concentration, size, exposure time, and cell type. The second proposed mechanism of GO-based killing bacteria is oxidative stress, which involves oxidation or dysfunction of cellular membranes. An accurate determination of the nature of physicochemical properties for 2D-GO which control oxidative stress based antimicrobial killing is lacking. Killing of bacteria via the extraction of lipid bilayers also has been proposed, but the mechanism of lipid extraction is in its infancy. As a result, more detailed studies are urgent. Therefore, a systematic collaborative study is urgently needed to determine the mechanism behind GO-based antibacterial activity.

Combating Bacteria Using 2D-MoS_2- and MoS_2-Based Heterostructures. Transition metal dichalcogenides (TMDs) are a unique class of 2D nanomaterials for the possible applications in drug delivery, phototherapy of cancer and bacteria, as well as its use as antibacterial wound healing agents.[10,24−31] Since TMDs have bandgaps in contrast to the zero bandgap of graphene, TMD has been studied for possible photonics, optoelectronics, and other applications.[10,24−31] After the first observation in 2014 by Yang et al.[26] that two-dimensional (2D) chemically exfoliated MoS_2 can be used as antibacterial materials, the interest has rapidly grown to develop MoS_2-based material for combating bacteria.[10,24−31] For this purpose, MoS_2 nanosheets were functionalized with either hydrophobic ligands or antimicrobial peptides.[10,24−31] Recently several reports indicate that the NIR-responsive MoS_2 nanosheets can be combined with functionalities for designing photothermal, photocatalytic, and chemical disinfection systems.[10,24−31] Similarly, we and others have demonstrated that by combining with other antibacterial nanomaterials such as silver, gold, and graphene oxide one can develop highly potent antibacterial nanocomposites using MoS_2-based heterostructure materials.[10,24−31] Yang et al.[26] have found that chemically exfoliated MoS_2 sheets have the capability to produce reactive oxygen species (ROS). They have suggested that antimicrobial activity for chemically exfoliated MoS_2 sheets is due to membrane damage and oxidation stress. Pandit et al.[30] demonstrated that functionalized chemically exfoliated MoS_2 can be used as a highly effective antibiotic agent against Gram-positive and Gram-negative pathogens as shown in Figure 6A−6E.[30] They have tested the antibacterial properties for exfoliated MoS_2 against MRSA and *P. aeruginosa* and their corresponding biofilms.[30] As shown in Figure 6A, in their design of positively charged MoS_2, the hydrophobicity was varied by changing the alkane chain length. Figure 6D shows the position of functionalized MoS_2 as an antibacterial agent compared to other materials. Pandit et al.[30] have reported minimum inhibitory concentration (MIC) for functionalized MoS_2 against MRSA and *P. aeruginosa*. Their reported data[30] indicate that for C1MoS_2 the MIC value is 1.88 ppm. On the other hand, the reported MIC values for C6MoS_2 and C8MoS_2 are 156 and 78 ppb, respectively.[30]

Their reported high antibacterial activity using functionalized MoS_2 is due to the net negative charge of bacterial surfaces and the positive charge of functionalized MoS_2. As a result, functionalized MoS_2 is highly effective to kill bacteria. As reported in Figures 6E, their experimental data indicate that functionalized materials generate less oxidative stress than exfoliated MoS_2. A detailed mechanistic study reported by Pandit et al.[30] indicates that ROS-independent oxidative stress generation as well as depolarization of the bacterial membrane are responsible for destroying bacteria using functionalized MoS_2.[30] Importantly, reported experimental data[30] demonstrated that by altering the hydrophobicity of positively charged MoS_2 one can tune the antibacterial pathway between oxidative stress and depolarization of the bacterial membrane.

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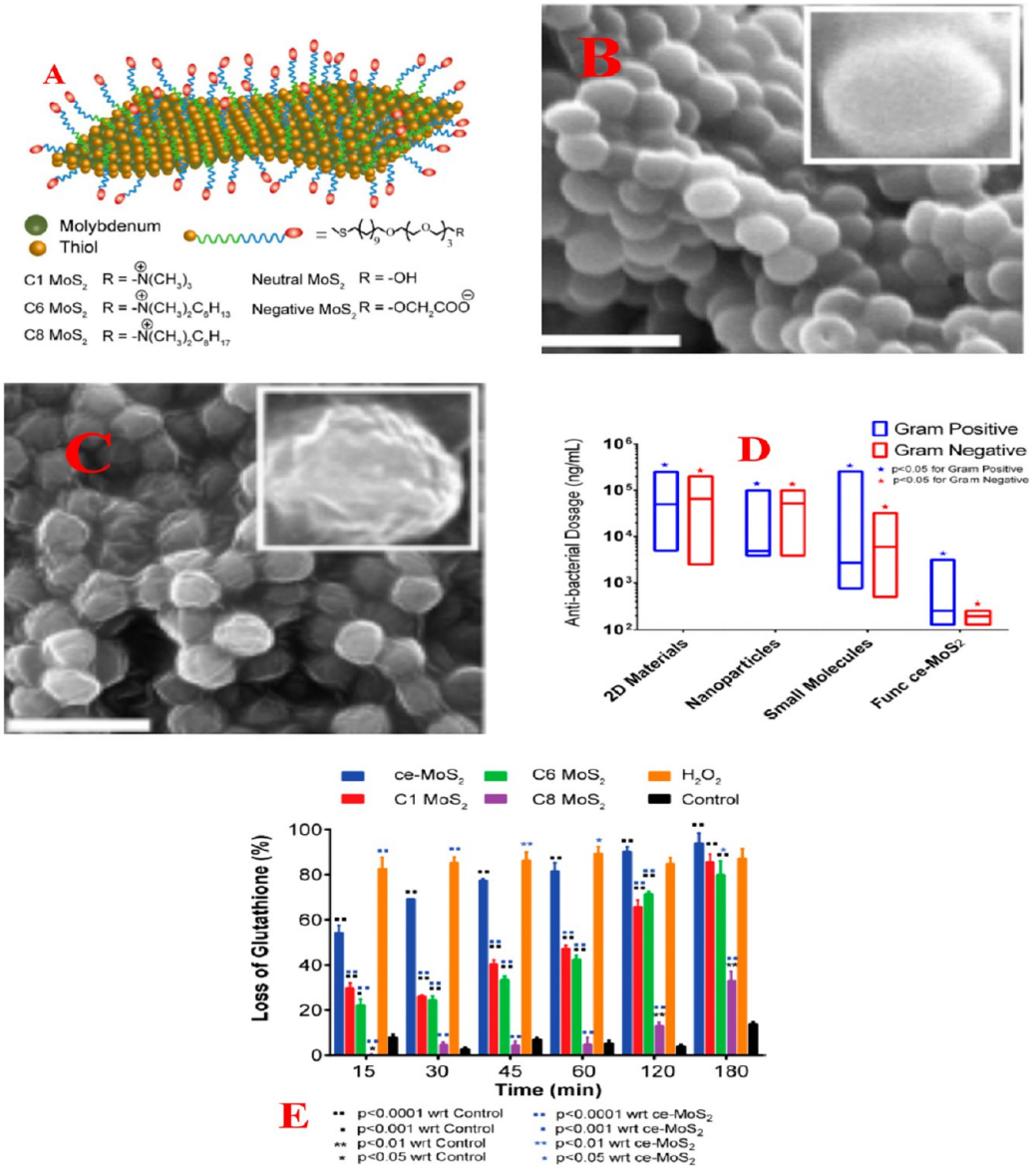

Figure 6. (A) Scheme shows the functionalized ce-MoS_2 with thiol ligands of varied charge and hydrophobicity. (B) SEM image of untreated MRSA without treatment using functionalized ce-MoS_2. (C) SEM images of MRSA after treating it with 2.5 × minimum inhibitory concentration (MIC) dosage of C8MoS_2 for 1 h. (D) Antibacterial dosage comparison of functionalized ce-MoS_2 with existing 2D materials, nanoparticles, and other small molecules. (E) Abiotic glutathione oxidation assay for quantification of oxidative stress generated (adapted with permission from ref 30. Copyright 2016, American Chemical Society).

Recently, we have reported[10] the design of the melittin antimicrobial peptide (AMP) attached MoS_2-based antibacterial agent for synergistic inactivation of 100% multidrug-resistant bacteria by the combined photothermal therapy (PTT), photodynamic therapy (PDT), and antimicrobial peptide (AMP) process, as shown in Figure 7A−7C. Our reported experimental data[10] show that using the synergistic killing mechanism of AMP-attached MoS_2 has the capability to kill 100% MRSA, *E. coli*, and KPN bacteria. In our design,[10] the MoS_2-based nanoplatform killed bacteria via an external NIR light-triggered combined photothermal and photodynamic mechanism. On the other hand, melittin antimicrobial peptide has been used to kill bacteria by pore formation as shown in Figure 7B.[10] As shown in Figure 7C, our reported experimental data demonstrated that only 28% of multidrug-resistant bacteria (MDRB) killing is possible using a MoS_2-based nanoplatform. On the other hand, only 20% of bacteria can be killed by the melittin antimicrobial peptide alone. Reported data[10] clearly show that 100% of bacteria can be killed using a nanoplatform with NIR light. The observed synergistic killing mechanism is due to the fact that in the presence of the PEG-MoS_2-AMP nanoplatform initially the melittin AMP makes pores on the surface of MDRB. Pores formed by AMP help to diffuse heat and ROS easily during PDT and PTT. Due to the above possible synergistic multimodal killing mechanism, 100% of MDRB was killed.[10] To understand better about the membrane pore formation, we have performed a bacterial ATP leakage experiment using the ATP determination kit.[10] Our reported data[10] indicate a high amount of leakage of cellular ATP even at the concentration of 2.8 μg/mL. Recently, Roy et al.[28] have reported the design of chitosan-exfoliated MoS_2 nanosheets (CS-MoS_2) as antibacterial agents. They have evaluated the antibacterial activity against both Gram-negative and -positive bacteria, which indicates that CS-MoS_2 nanosheets have the

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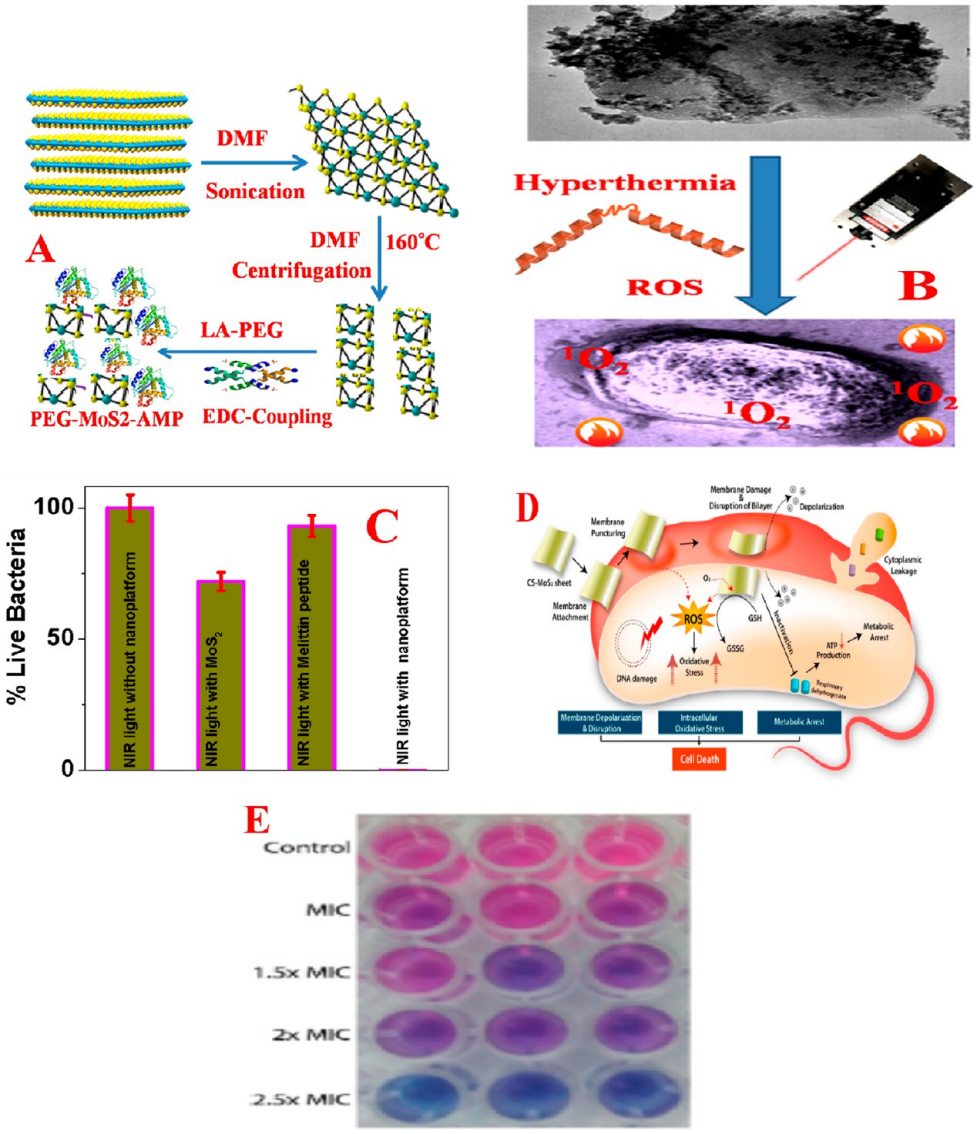

Figure 7. (A) Scheme shows the synthetic procedure that was used for the development of an antimicrobial peptide attached MoS_2 nanoplatform. (B) Scheme shows the development of antibacterial for bacteria using an antimicrobial peptide attached MoS_2 nanoplatform via the combined PTT, PDT, and AMP process. (C) KPN killing efficiency using only NIR light, PEG-MoS_2 nanoflakes and light, melittin AMP and light, and PEG-MoS_2-AMP nanoplatform and light (adapted with permission from ref 10. Copyright 2019, American Chemical Society). (D) Scheme shows the possible mechanism for chitosan-exfoliated MoS_2 nanosheets based antibacterial activity. (E) Effect of chitosan-exfoliated MoS_2 nanosheets on the viability of the *S. aureus* biofilm (adapted with permission from ref 28. Copyright 2019, American Chemical Society).

capability for growth inhibition of both Gram-negative and Gram-positive bacteria in a concentration- and time-dependent manner, as shown in Figure 7D−7E.[28]

They have determined MIC and minimum bactericidal concentration (MBC) of the CS-MoS_2 nanosheets against both *E. coli* and *S. aureus* as shown in Figure 7E. Their reported data[28] indicate that the MIC and MBC values of CS-MoS_2 nanosheets against *E. coli* are 30 and 60 μg/mL, respectively. Similarly, the MIC and MBC values for *S. aureus* are found to be 90 and 120 μg/mL, respectively.[28] From their reported data[28] they have concluded that due to the presence of a thick peptidoglycan layer surrounding the Gram-positive *S. aureus* it required a higher concentration of CS-MoS_2 for achieving antibacterial activity.[28] Experimental data reported by Roy et al.[28] indicated that the CS-MoS_2 nanosheets induced bacterial cell death through a combined action of membrane damage, metabolic inactivation, and oxidative stress. The detailed mechanistic study indicates that the antibacterial activity of CS-MoS_2 nanosheets happens through a multistep process, and these are membrane damage, metabolic inactivation, and oxidative stress.[28] They have concluded that CS-MoS_2 nanosheets can probably be used as antibacterial coatings, wound dressings, and ultrafiltration membranes for potential biomedical and environmental applications.[28]

Cao et al. have reported[29] the design of a poly(dimethyldiallylammonium chloride) (PDDA)-Ag+-Cys-MoS_2 heterostructure and their antimicrobial properties. Their reported data as shown in Figure 8A−8D indicate that the PDDA-Ag+-Cys-MoS_2 exhibited enhanced broad-spectrum antibacterial activity for Gram-negative *E. coli* and Gram-positive *S. aureus*.[29] On the other hand, their reported data show extremely low antibacterial ability for equivalent amounts of AgNP or $AgNO_3$ solution. Reported *in vitro* and *in vivo* antibacterial experiments indicate that cationic polyelectrolyte

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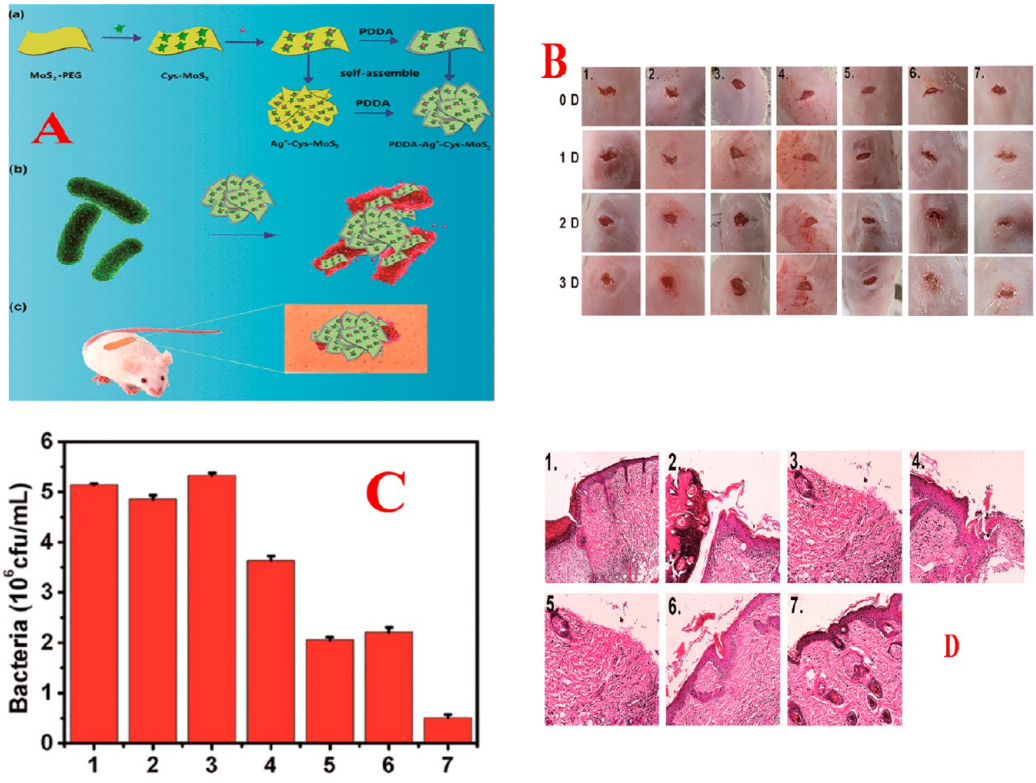

Figure 8. (A) Design of the poly(dimethyldiallylammonium) chloride (PDDA)-Ag^+-Cys-MoS_2 depot for antibacterial applications. (B) Photographs of wound on the mice from the seven groups based on treatment with PBS buffer, $AgNO_3$, AgNPs, PDDA, Cys-MoS_2, Ag^+-Cys-MoS_2, and PDDA-Ag^+-Cys-MoS_2, respectively. (C) Number of the surviving bacteria in the wound tissue of each treatment. (D) Photomicrographs showing section of skin tissues with H&E staining (adapted with permission from ref 29. Copyright 2017, American Chemical Society).

promoted the adhesion of PDDA-Ag+-Cys-MoS_2.[29] From the experimental data, they have concluded that PDDAAg+- Cys-MoS_2 could release large amounts of Ag^+ ions at the cell walls of microorganisms.[29] As shown in Figure 8A−8D, for *in vivo* experiment, Cao et al. have used the infected wound model. For this purpose, the back of the mice was slashed and injected with 1×10^6 of MRSA.[29] In the next step, the mice were divided into seven groups, based on treatment with PBS buffer, $AgNO_3$, AgNPs, PDDA, Cys-MoS_2, Ag^+-Cys-MoS_2, and PDDA-Ag^+-Cys-MoS_2.[29] Their experimental data, as shown in Figure 8, show that for control groups a fragmentary epidermal layer appeared on the wound after 3 day treatments.[29] On the other hand, the intact epidermal layer emerged on the wound treated with PDDA-Ag+-Cys-MoS_2 dressing for 3 days.[29] Their reported data clearly show that PDDA-Ag+- Cys-MoS_2 exhibited the best antibacterial effect and wound healing.[29]

In this section, we have discussed 2D-MoS_2 and heterostructure-based design of antibacterial strategy for killing bacteria. We have highlighted some of the proposed antibacterial mechanisms and latest developments in the practical antimicrobial applications for TMD and TMD-based heterostructures. Since 2D-MoS_2-based antibacterial agent design is in the very early stages, the antibacterial mechanism has not been completely understood. Computational simulation studies are very important to analyze the interactions between 2D-TMD materials and biological components which will enable the determination of the possible mechanism. As a result, in-depth investigations are urgently needed to find out the mechanisms and different parameters influencing the antibacterial activity for TND-based materials.

Combating Bacteria Using 2D-MXenes and Heterostructures. The emerging MXenes, a new family of multifunctional 2D materials, exhibit metallic conductivity, hydrophilic nature, and unique physiochemical performances.[32−35] As a result, in the past few years, transition metal carbides, nitrides, and carbonitride-based MXenes have been introduced as novel inorganic nanosystems for biologic and biomedical applications.[32−35] After, the first MXene, multilayered Ti_3C_2, was developed in 2011,[32] a series of 2D MXenes were designed.[33−35] For the last eight years, few groups have explored possible applications in energy storage, theranostic material, chemical and biomedical sensors, etc.[33−35] After the first observation in 2016 by Rasoo et al.[33] that two-dimensional $Ti_3C_2T_x$ MXenes can be used as antibacterial materials, the interest has rapidly grown to develop MXene-based material for combating bacteria.[33−35] Rasoo et al.[33] tested the antibacterial properties of Ti_3C_2Tx against *Escherichia coli (E. coli)* and *Bacillus subtilis (B. subtilis)*. Their reported data as shown in Figures 9B−9D indicate that Ti_3C_2Tx exhibits a higher antibacterial efficiency toward *E. coli* and *B. subtilis* comparable with GO.[33] As shown in Figure 9D, their experimental data on concentration-dependent antibacterial activity indicate more than 98% bacterial cell viability in the presence of 200 μg/mL of Ti_3C_2Tx.[33] Antibacterial mechanistic investigation data by Rasoo et al.[33] show the damage to the cell membrane which kills bacteria.

Shamsabadi et al.[34] have reported size-dependent antibacterial properties of MXene. For this purpose, they have tested antibacterial activity for nanosheets with lateral sizes of 0.09, 0.35, 0.57, and 4.40 μm against *Escherichia coli* and *Bacillus subtilis* bacteria.[34] Their reported data indicate that smaller nanosheets exhibit higher antibacterial activities against both

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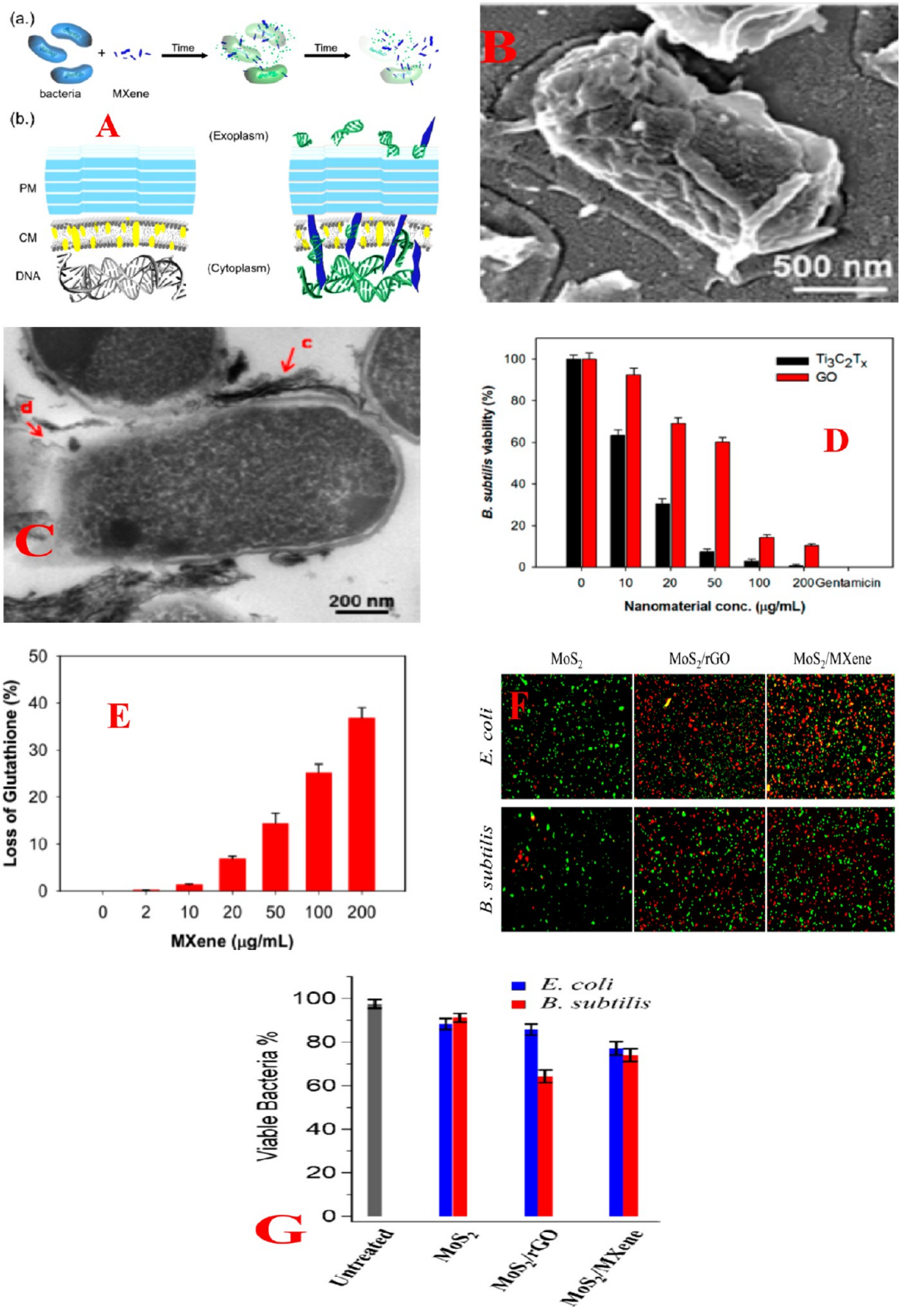

Figure 9. (A) Schematic representation of proposed antibacterial mode-of-action of Ti_3C_2Tx MXene nanosheets (adapted with permission from ref 34. Copyright 2018, American Chemical Society). (B) SEM images of the *B. subtilis* treated with 50 μg/mL of Ti_3C_2Tx. (C) The cell wall stripped down after exposure to Ti_3C_2Tx nanosheets. (D) Cell viability measurements of *B. subtilis* treated with Ti_3C_2Tx and graphene oxide (GO) in aqueous suspension. (E) Time-dependent glutathione (0.4 mM) loss after incubation for 4 h with Ti_3C_2Tx (200 μg/mL) (adapted with permission from ref 33. Copyright 2016, American Chemical Society). (F,G) Antibacterial activity of MoS_2, MoS_2/rGO, and MoS_2/MXene nanomaterials against *E. coli* and *B. subtilis* bacteria. Fluorescence imaging (F) and flow cytometry (G) results of bacteria treated with 100 μg/mL of the nanomaterials for ca. 3 h in the dark. In fluorescence images, the live bacteria are green (SYTO9-stained), and the dead bacteria are red (PI-stained). 400× magnification was used (adapted with permission from 35. Copyright 2018, American Chemical Society).

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bacteria.[34] The schematic representations of the proposed antibacterial mode-of-action of Ti_3C_2Tx MXene nanosheets are shown in Figure 9A. Reported antibacterial mechanism studies indicate that interactions between the sharp edges of the Ti_3C_2Tx MXene nanosheets and bacteria membrane play an important role in antibacterial properties of the nanosheets.[34] From the experimental data, Shamsabadi et al.[34] have concluded that MXene damages the bacterial cell wall significantly in less than 3 h by releasing DNA from the cytosol. Alimohammadi et al.[35] have reported the comparison of antibacterial activity of vertically aligned different 2D heterostructures such as MnO_2/GO, MoS_2/rGO, and MoS_2/MXene. Experimental results by Alimohammadi et al.[35] show that a vertically aligned 2D nanosheet motif exhibits higher antibacterial activity than 2D nanomaterials, as shown in Figure 9F−9G. Their reported experimental data indicate that the number of viable bacteria became 90% when *B. subtilis* was treated with MoS_2.[35] On the other hand, the number of viable bacteria became 60% and 75%, when *B. subtilis* was treated with MoS_2/rGO and MoS_2/MXene, respectively.[35]

In this section, we have discussed 2D-MXene and heterostructure-based design of antibacterial material for killing bacteria. We have highlighted very recent developments in the antimicrobial applications for 2D-MXene and 2D-MXene-based heterostructures. Since only in the past few years antibacterial properties for 2D-MXene have been realized the antibacterial mechanism is poorly understood, where further studies are very important. A systematic collaborative *in vivo* experimental study is highly necessary to understand the environmental impacts and the interaction between 2D-MXene with different organisms, before it can be used for society.

Although we have only highlighted 2D-GO, MoS_2, MXene, and heterostructure material-based antimicrobial strategies, some other 2D materials such as layered double hydroxides (LDHs), hexagonal boron nitride (BN), 2D metal oxides, and 2D kaolinite are also emerging as potential antibacterial agents.[4−9]

Summary. In conclusion, in the current mini-review we have discussed recent advancements on 2D-GO, MoS_2, MXene, and heterostructural material-based antimicrobials, which have the capability to be used for disinfection of bacteria *in vivo* and *ex vivo* applications. Reported data from several groups have demonstrated that the tunable surface functionality of 2D-GO, MoS_2, MXene, and heterostructures has the ability to provide a versatile platform to combat drug-resistant bacterial infections. We have discussed how the material design can be tailored for heterostructure-based antimicrobial nanocomposites to tackle the multidrug-resistant problem. The current state of the art 2D and heterostructure material based animal model data show that the nanomaterial has strong potential to treat topical skin infections in the near future. We hope that the current mini-review will provide researchers to realize the potential of 2D multifunctional materials for combating bacteria.

Challenges. Although from the reported data we can realize that 2D-GO, MoS_2, MXene, and heterostructures have the capability for combating bacteria, it is still too early to apply 2D and heterostructure-based antibacterial material for real life clinical applications. Large-scale and low-cost design of 2D and heterostructure-based antibacterial material with high reproducibility is very important for practical use, which is lacking until now. The fabrication process needs to be designed in such a way that 2D and heterostructure-based antibacterial material should retain activity in complex biological media. Since for clinical applications 2D-GO, MoS_2, MXene, and heterostructural material-based antimicrobials can be given through either skin contact, oral, or intravenous injection, a thorough *in vivo* model must be evaluated to better understand their potential toxicity, clearance, and metabolism. We really need to understand the biodegradability of sheet-structured 2D materials inside the body. The central questions we need to determine is whether intravenously injected 2D-GO, MoS_2, MXene, and heterostructural material-based antimicrobials accumulate in the colon, lung, bone marrow, liver, spleen, and lymphatics? The pharmacological profiles of 2D and heterostructure-based antibacterial material are essential for the clinical translation, which is missing now. Interdisciplinary research evaluating these aspects needs to be performed very carefully, which will allow us to establish 2D and heterostructure nanomaterials as effective next-generation antimicrobials for bacteria.

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