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Review article

Emerging trends and future challenges of advanced 2D nanomaterials for combating bacterial resistance

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ABSTRACT

The number of multi-drug-resistant bacteria has increased over the last few decades, which has caused a detrimental impact on public health worldwide. In resolving antibiotic resistance development among different bacterial communities, new antimicrobial agents and nanoparticle-based strategies need to be designed foreseeing the slow discovery of new functioning antibiotics. Advanced research studies have revealed the significant disinfection potential of two-dimensional nanomaterials (2D NMs) to be severed as effective antibacterial agents due to their unique physicochemical properties. This review covers the current research progress of 2D NMs-based antibacterial strategies based on an inclusive explanation of 2D NMs' impact as antibacterial agents, including a detailed introduction to each possible well-known antibacterial mechanism. The impact of the physicochemical properties of 2D NMs on their antibacterial activities has been deliberated while explaining the toxic effects of 2D NMs and discussing their biomedical significance, dysbiosis, and cellular nanotoxicity. Adding to the challenges, we also discussed the major issues regarding the current quality and availability of nanotoxicity data. However, smart advancements are required to fabricate biocompatible 2D antibacterial NMs and exploit their potential to combat bacterial resistance clinically.

1. Introduction

1.1. The growth of bacterial resistance: a global challenge

The emergence of multi-drug resistance among bacteria is a grave concern for medical hospitals dealing with infectious diseases [1]. Multidrug-resistant (MDR) bacteria, also known as super-bugs, are one of the major sources of global crisis (apart from war, starvation, and climate change). The increasing morbidity and mortality rate of infected individuals negatively impacts the outcome of a wide range of clinical categories, including the intensive care unit patients undergoing surgery, cancer treatment, and organ transplantation [2]. In the last two decades, there has been a rapid decline in the development of advanced antibiotics, leading to millions of deaths every year by leaving no option to treat drug-resistant bacteria [3]. According to the World Health Organization, by the year 2050, drug-resistant bacteria could kill 10 million people each year if researchers cannot find an alternative solution to tackle infectious bacteria; which is higher than the number of people currently dying from cardiovascular disease and cancer. The above facts have triggered global enterprises to develop novel antibacterial substances for targeted bacterial inactivation or killing [4]. In 2021, the WHO (World Health Organization) and GLASS (Global Antimicrobial Resistance and Use Surveillance System) Report stressed antibiotic resistance as a global challenge against anti-human immunodeficiency virus and anti-tuberculosis drugs, which has emerged as a public health threat due to the misuse or overuse of antibiotics that further exacerbated the progress of new antimicrobial therapeutics entering the antibiotics pipeline. In the interim, a descriptive timeline of antibiotic discovery and antibiotic resistance from 1930 to 2020 [5,6] is shown in Fig. 1. Trail developmental procedures often took place to cure antibiotic resistance against antimicrobial therapy, resulting in the emergence of heritable resistance to antibiotics through horizontal gene transfer (HGT). This can be accomplished through transduction, transformation, bacterial conjugation, and biofilm formation among bacterial

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communities and may spread drug resistance. Planktonic or free-floating bacteria are the major culprits in multiple health menaces, such as sepsis [1,5]. The generalized bacterial resistance mechanisms against antibiotics are illustrated in Fig. 2A and B. These resistance mechanisms help them evade antibiotic treatment and differ from the intrinsic genetically acquired resistance genes. However, these resistance ways also include the transfer of resistance genes, as in the case of HGT. Other resistance mechanisms include target modification, deactivating enzymes, antibiotic removal by efflux pumps, reduced uptake of antibiotics due to the blocked channel proteins, and entrapment of antibiotics in extracellular polymeric substances (EPS) exhibiting biofilm resistance; the more detailed discussion on tackling resistance mechanisms is covered in section 1.3. Covering the variety of antibacterial treatments and major challenges in conventional antibiotic therapy with combating strategies to overcome this worldwide concern. These are the generalized mechanisms of antibiotic resistance commonly found among bacterial cells and communities. However, newer resistance ways might soon emerge if we keep using excessive antibiotics and damaging the food chain.

1.2. Need for innovative approaches

These bacterial communities cause an acute level of infections and become more challenging to treat due to increasing rates of acquired antibiotic resistance. This challenge gets amplified when bacteria form

Fig. 1. Antibiotic discovery and antibiotic resistance, a descriptive timeline of bacterial resistance against antibiotics and NPs. Updated and Reproduced with permission [6]. Copyright © 2021, American Chemical Society.

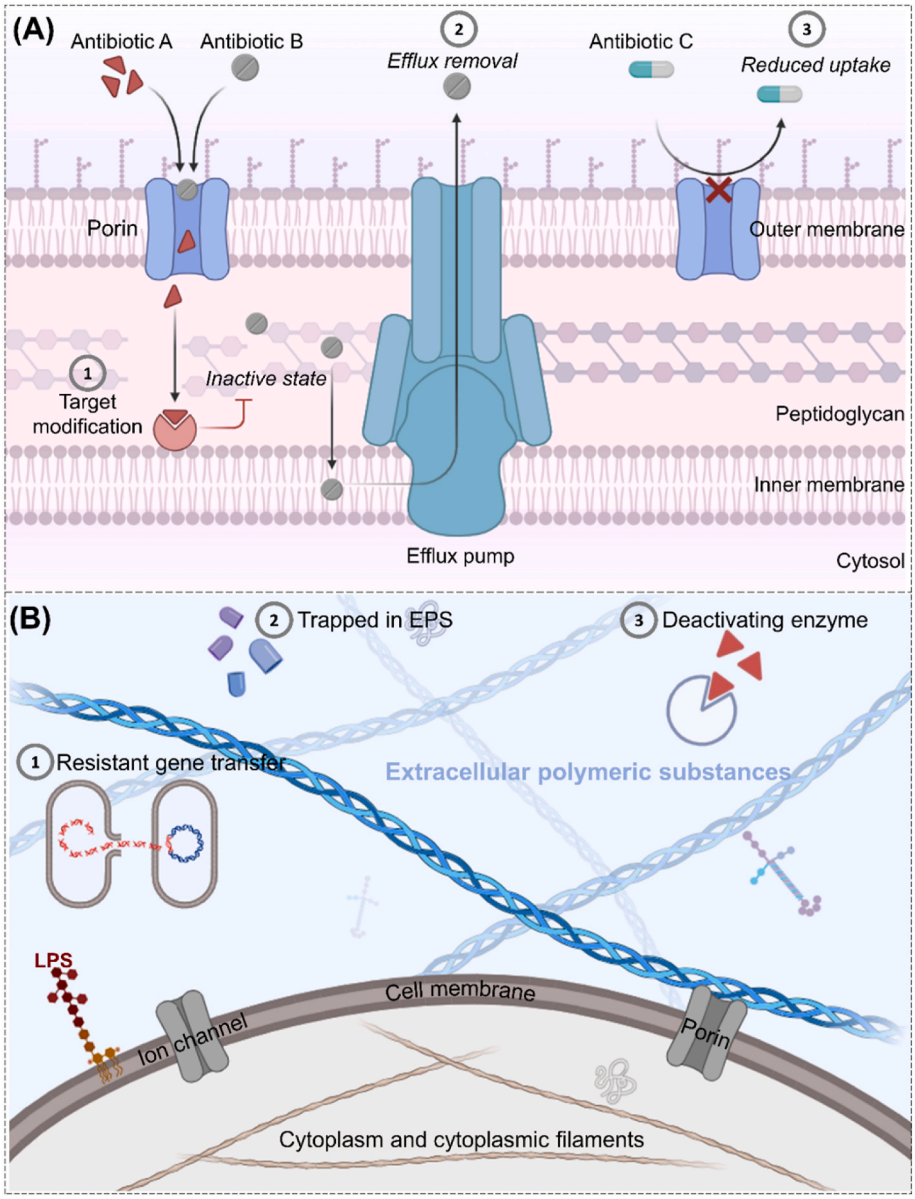

Fig. 2. **(A)** Generalized antibiotic mechanisms exhibited by bacterial cells *via* target modification affecting different cellular metabolic states, removal of antibiotics with the help of efflux pumps, reduced uptake of antibiotics by losing access to the cell membrane, **(B)** Biofilm resistance mechanisms include transfer of resistance genes within and across the bacterial communities, adsorption and entrapment of antibiotics in the EPS layers restricting their penetration, deactivating enzymes deactivate and modify the antibiotics and remove them from their system. Created with BioRender.com.

biofilms and cause recurring maladies, which are highly associated with chronic infections. Biofilm acts as a protective barrier in bacterial infections (protects bacterial cells, restricts penetration of antibiotics, and resists gene transfer). It complicates the treatment during antimicrobial therapy, such as endocarditis, osteomyelitis, and chronic wounds. Moreover, biofilm-associated antibiotic resistance differs from the acquired resistance shown by cells [7]. The most prevalent biofilm-forming bacteria related to human biology (diseases) are *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* (*S. epidermidis*), *Escherichia coli* (*E. coli*), *Enterococcus faecalis* (*E. faecalis*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Streptococcus viridans* (*S. viridans*), *Klebsiella pneumoniae* (*K. pneumoniae*), and *Proteus mirabilis* (*P. mirabilis*), among few others. These Gram-negative and Gram-positive bacteria can develop biofilm layers on internal medical devices (including prosthetic joints, catheters, and mechanical heart valves), which execute constant infections distinguished by their slow progress [5]. Secondly, both Gram-positive and Gram-negative bacteria employ quorum-sensing (QS) to regulate bacterial resistance against a wide range of antibiotics. However, the composition of the systems differs noticeably. QS and biofilm development are two closely interrelated processes; what is more important is that the QS system performs an important role by regulating the biofilm formation (*via* drug efflux pumps) and is involved in the synchronal expression of target genes across a bacterial population by communicating cell to cell [8]. The QS system releases chemical signal molecules required for cell-to-cell communication, known as autoinducers (AIs). Gram-positive QS systems mainly release autoinducing peptides (AIPs), while Gram-negative QS systems release N-acylated homoserine lactones (AHLs). Also, bacterial species employ a wide variety of QS systems during infection. However, there are a few exceptions to pervasive QS systems, including the LuxS/AI-2 system, but it is debatable whether this system has the same role among all species. The wide variety of QS systems has been studied in Gram-positive bacteria (including *S. aureus*, *Listeria monocytogenes*, *E. faecalis*, *S. epidermidis*, and *Clostridioides* species, among few

others) and Gram-negative bacteria (*P. aeruginosa*, *Vibrio fischeri*, and *Acinetobacter baumannii*) [9]. Bacterial resistance is one of the major global challenges that has aggravated difficulty in disease prevention and simultaneously raised mortality rates due to the excessive use of drugs. On one side, the QS system involves the regulation of biofilm formation, sporulation, drug resistance, and expression of several virulence factors, including disinfectant tolerance and toxin production. On the other hand, the QS system can be transformed and used for quorum quenching to resolve the problem of drug resistance with the help of nanomaterials that interfere with the QS system itself. The nanomaterials are responsible for hindering the exchange of information between specific bacteria that reduce the target expression of hazard factors (known as quorum quenching) [10].

1.3. Traditional antibacterial mechanisms vs nanomaterials-based antibacterial mechanisms

1.3.1. Antibacterial mechanisms by antibiotic treatment

Up to 145 antibiotics have been approved for clinical studies in the past century. Antibiotics can differentiate between bacteria and mammalian cells and display specific targets according to their biological functions. These specific targets also determine the type of antibacterial or antimicrobial mechanisms, including inhibition of cell wall synthesis, depolarization of cell membrane, inhibition of protein synthesis, arresting nucleic acid synthesis, and metabolic pathways. The antibacterial mechanism of cell wall inhibition is casually reported in β-lactams (such as cephalosporins, ceftaroline, and ceftobiprole) by covalent binding of penicillin-binding proteins for blockage of peptidoglycan biosynthesis. The antimicrobial peptides known as AMPs (including linear-mycins, cecropin, and polymyxin) have a serious impact on the depolarization of cell membranes by interacting with LPS and phospholipids. Whereas clinically investigated antibiotics (such as tetracyclines, macrolides, chloramphenicols, and aminoglycosides) block the synthesis of essential proteins by targeting the main functional centers of ribosomes, i.e., the 30S and 50S subunits along with ribosome exit tunnel. Another group of antibiotics, known as Quinolones, inhibit critical enzymes required in nucleic acid synthesis by preventing DNA unwinding and duplication. These main enzymes are DNA gyrase and topoisomerase IV. Furthermore, it has been stated in several studies that some antibiotics take over the bacterial metabolic process by binding to their target components or producing toxic byproducts to inhibit the substrate-specific metabolic pathways [11].

1.3.2. Challenges in traditional antibiotic therapy

Pathogens acquire different mechanisms to execute resistance against conventional antibiotics. These mechanisms involve overexpression of efflux pumps to get rid of antibiotics from bacteria, acquisition of unconventional metabolic pathways to replace drug-inhibited pathways, decreased permeability of the bacterial cellular membrane to restrict antibiotics access to the target sites, enzymatic modification of antibiotics and their degradation, overexpression of active enzymes, alteration of antibiotic target sites, and transfer of antimicrobial resistance genes by QS within biofilm consortium [12,13]. Biofilms play a significant role in human infectious diseases, which makes it difficult to resist the mounting severity of infections caused by biofilm-embedded bacteria. Antibacterial resistance mechanisms involve two major resistant strategies commonly used by individual bacterial species and bacterial communities.

1. *MDR biofilm strategies* derived from NMs affect the efflux pumps' performance and interfere with QS signaling molecules within the biofilm consortium. Biofilm formation on material surfaces is ubiquitous due to the constant bacterial colonization. Surface-colonized bacteria pose serious economic and health concerns and threats to society. In the current challenging field, the most important strategy is the incorporation of antibacterial nano-components within or on the surface of NMs *via* coatings to prevent bacterial adhesion and eradicate bacterial cells after penetrating the biofilm matrix. The antibacterial metal nanostructures have offered a promising bactericidal strategy in combatting MDR pathogens, which have particularly received significant attention in academia, medicine, and the pharmaceutical industry [14,15].
2. *Plasmid-mediated MDR* is one of the most obstinate complications in treating infectious diseases. Bacterial plasmids contain ARGs and acquire catabolic pathways for lactose utilization and hydrocarbon degradation [14]. These plasmids can be transferred to other bacterial species or strains through QS, unlike the division of chromosomal materials from generation to generation. However, plasmid curing is a technique to manipulate plasmid genes during cellular replication in bacteria. Although no such current technology is reported to date, the practice of customized NMs as plasmid-curing tools may be the future target to circumvent the conjugational transfer of antibiotic-resistant plasmids and reduce their proliferation within the biofilm consortium [16].

2. Nanomaterials: Types and antibacterial properties

2.1. Types of nanomaterials of different dimensions and compositions

This section will briefly discuss the few common antibacterial sources known to have relatively moderate to significant antibacterial properties. These materials include various types of nanoparticles (metal, metal oxides, metal clusters, metal-organic-frameworks, liquid metal, carbon dots) and small-sized antimicrobial components that possess similar antibacterial properties (e.g., polymers, supramolecular nanosystems, chiral biomolecules, and other biomolecules). Over the last two decades, nanomaterials, including nanoparticles (0D), nanorods (1D), nanosheets (2D), and hybrid (3D) amalgam, have captivated huge interest in biomedicine by showing significant advantages of target-specific delivery, bio-imaging, and antimicrobial applications [17].

2.1.1. Metal and metal oxide NPs

Metal and metal oxide NPs can differentiate between prokaryotic (bacteria) and eukaryotic (mammalian) cells through the metal transport system and metalloproteins of bacterial cells. These nanoparticles exhibit a high surface-to-volume ratio and offer long-term antibacterial and biofilm inhibition. Generally, they possess antibacterial properties and demonstrate multiple antibacterial mechanisms through the generation of ROS, targeting physical cellular structures, provoking metabolic pathways, and halting DNA synthesis, eventually causing cell death [18]. Combined with oxygen to fabricate a metal oxide, these metal elements showed many diverse physiochemical and functional properties. Moreover, metal oxides interact with bacterial cells differently based on electrostatic forces that alter the bacterial cell wall, enzymes, and DNA *via* ROS storming. These metal and metal oxide NPs usually kill bacterial cells *via* several modes of action, including interactions with the phospholipid bilayer of bacterial cell walls, adhering to cytosolic proteins of bacterial cells (including DNA and enzymes), and causing irreversible physical damage *via* ROS generation. Examples of antibacterial nanoparticles are Ag NPs, Au NPs, Fe NPs, Ga NPs, ZnO NPs, MgO NPs, and TiO_2 NPs, among many others, exhibiting their unique bactericidal approach against various Gram-positive bacteria and Gram-negative bacteria. After witnessing such distinction over their conventional counterparts, bacterial cells can form a resistance against these types of NPs in case of multiple gene mutations within the cell or horizontal gene transfer across the bacterial communities. However, these nanoparticles are associated with metal cytotoxicity [19].

2.1.2. Metal nanoclusters

They have been familiar as a new group of molecular-like aggregates comprising a few to several hundred metal atoms and exhibiting a smaller size comparable to the Fermi wavelength of electrons. Also,

metal nanoclusters exhibit idiosyncratic physicochemical properties such as HOMO-LUMO transition, robust Stokes shift, sturdy photoluminescence, and higher biocompatibility. They have received increasing attention in many fields as they fill in the missing gap between single metal atoms and plasmonic metal NPs. From the antibacterial application point of view, these metal nanoclusters (NCs) can be divided into gold NCs, copper NCs, silver NCs, alloy NCs, and other related nanocomposites. Among these NCs, copper NCs and silver NCs have shown outstanding antibacterial effects since both of these elements have intrinsic broad-spectrum antibacterial propensities [20]. In addition to their properties and application performance, these NCs possess intricate molecular structures and are sensitive to their chemical nature. Two related metal nanoclusters with a difference of only a few atoms or even one atom difference will show quite different or contradictory behaviors. For example, Au_{15} NCs exhibit a competitive Langmuir−Hinshelwood catalytic behavior, while slightly larger Au_{18} NCs and Au_{25} NCs show a noncompetitive catalytic behavior similar to AuNPs [21].

2.1.3. MOFs-based nanozymes

Metal-organic frameworks (MOFs) exhibit distinguished characteristics and fill the functional gap between natural enzymes and nanozymes. These characteristics include enzyme-like mimetic activity and unique structural properties (crystalline porosity, tunable pores, and large surface area with uniformly dispersed active sites). These complexes came into existence due to the integration of natural enzymes and their active moieties into nano-frameworks or some nanomaterials that intrinsically display enzyme-like activities [22]. Owing to their intrinsic catalytic properties, most of them are employed for biomedical applications and are subjected to the oxidoreductase family of natural enzymes. The oxidoreductase family majorly comprises peroxidase, oxidase, catalase, and superoxide dismutase. Thus, MOFs-based nanozymes are also categorized as four major oxidoreductases [23,24]. Like other conventional organic and inorganic nanomaterials, MOFs also contribute to the potential nanotoxicity as they are composed of metals (nanoparticles or clusters) and other organic framework constituents. The most incorporated metal ions in MOF synthesis are Zn^{2+}, Fe^{2+}, Fe^{3+}, Cu^{2+}, Cd^{2+}, Co^{2+}, and $Ni^{2+,}$ among a few others. Most of these metal ions are non-biodegradable; Cd^{2+} possesses carcinogenic properties, whereas Zn^{2+} and Fe^{2+} play an important role in various cellular functions and possess minimum nanotoxicity [24]. In addition, MOFs with micropore structures showed a decline in catalytic efficiency as they do not accommodate larger molecule substrates intended to be an important part of the catalytic reaction. Therefore, fabricating MOFs with mesoporous macropore structures is considered more practical, specifically for combined or synergistic antimicrobial approaches.

2.1.4. Liquid metals (LMs)

Liquid metals and their metal alloys proffer fluidity at body temperatures. Their liquid nature is due to the electron-rich metallic cores with interfaces that can be easily manipulated as they can tightly bind their electrons to the atomic nucleus. These are francium, gallium, rubidium, and cesium. Gallium (Ga) has become a fascinating element because of its antimicrobial impact with low toxicity and melting point (29.8 °C). Ga alloys exhibit certain tailorable properties due to the amalgamation of various metals, such as magnetic permeability, phase shifting, chemical reactivity, catalytic activity, and surface composition [25]. Moreover, Ga nanoparticles showed antibacterial and anti-inflammatory properties against infected cells. Overall, this small yet unique group of metals can offer advantages in designing antimicrobial systems relative to solid metal nanoparticles and could be the auxiliary way to sidestep the emergence of MDR pathogens [26].

2.1.5. Carbon dots (CDs)

Carbon dots are one of the newest types of carbon-based NMs exhibiting peculiar optical features, lower toxicity, and significant biocompatibility, and require simple and cheap modification and functionalization steps. They were designed as multipurpose antibacterial tools with functions for imaging, targeting, elimination, and other functions in recent times [27]. CDs possess intrinsic antibacterial qualities and can adsorb onto bacterial cell walls *via* electrostatic interactions, facilitating biological isolation and preventing bacterial growth. Also, they can inhibit biofilm formation *via* apoptosis and halt DNA and RNA synthesis by modifying their secondary conformations. Many factors inhibit bacterial growth when CDs interact with bacterial cells, even without light irradiation (photoexcitation) [28]. In some cases of antimicrobial treatment, light irradiation is necessary to exert their full potential against MDR bacterial species. For example, as photosensitizers, CDs have greater potential to fight against antimicrobial resistance during antimicrobial photodynamic therapy (APDT). They have been used in clinical applications for wound healing, biomaterial implants, and antimicrobial coatings [29].

2.1.6. Polymers with conjugated nanoparticles

Polymers are the small molecules of repetitive monomer units, protecting humans for nearly a century from deadly bacterial infections since the discovery of penicillin by Alexander Fleming. These synthetic antimicrobial polymers practically replaced naturally occurring antimicrobial peptides by mimicking their functional mechanisms, and they can potentially end multidrug resistance bacterial diseases shortly. The specific and required qualities can be harnessed by regulating their chemical and structural properties and strategical execution in combinational therapies [30]. In these combined formulations, antibiotics are loaded within the synthetic polymer *via* encapsulating the polymeric nanostructures or conjugated to their polymer chains. Such combinations not only improve the antibacterial efficiency but also increase the lifetime of antibiotics [31].

2.1.7. Supramolecular antibiotic delivery nanosystems

Supramolecular structures derived from the chemical exploitation of molecules through non-covalent interactions (hydrogen bonding, π–π interactions, van der Waals interactions, hydrophobic interactions, and metal chelation, *etc*.) with reversible and tunable properties [32]. The supramolecular macrocycles exhibit not unique structures and dynamic nature but also demonstrate versatile functionality and encourage the formation of host-guest complexes when used *in vivo*. Several supramolecular macrocycles contribute to fabricating different antibacterial materials, including pillararenes, cucurbiturils, cyclodextrins, and calixarenes, among a few other macrocycles that might facilitate the development of contemporary medicines. Modern chemical strategies adapted a multipurpose supramolecular gelatin-based antibiotic delivery nanosystem that kills bacterial cells and absorbs the bacterial exotoxins by relieving the symptoms after bacterial infection [33].

2.1.8. Chiral biomolecules functionalized nanoscaffolds

Molecular chirality has been considered an important aspect of drug design, toxicity, metabolism, and pharmacokinetics. Most drugs are designed in enantiomerically pure form, considering their effectiveness and safety for human use. Chirality plays a vital role in predicting the significance of nanomedicine and should be considered while developing novel biomaterials and nanoscaffolds [34]. Chirality is widespread; for instance, DNA, RNA, L-amino acids, and D-carbohydrates are all the fundamental building blocks of living systems owing to evolution. There is a clear chance of two possible enantiomeric forms, but evolution has selected only one based on its intended use [35]. They have been used to assemble various NMs with specific configurations *via* polypeptide conjugation to design materials with specific physicochemical properties. For example, glutathione has been used to conjugate gold nanorods into chiral nano-assemblies, and their optical properties can also be adjusted easily by changing the glutathione concentration. However, peptides could not fill the current void in antimicrobial drug development as they are ineffective against resistant

microbial communities. Also, their stability and toxicity concerns limit their market value for topical and non-invasive treatments [36].

In general, these above antimicrobial scaffolds include a wide range of materials, starting from polymers, biopolymers, peptides, metals, metal alloys, ceramics, carbon materials, antibiotics, antiseptics combinatorial strategies, and include an inclusive discussion on their antimicrobial mechanisms and toxicological aspects to ensure their practical use from *in vitro* studies to clinics. These studies mostly include two main antimicrobial methods that characterize scaffolds' antimicrobial and antibiofilm nature. These scaffolds do not display the physicochemical characteristics of nanoparticles. However, they sometimes contain nanoparticles as fillers and exhibit similar biological applications, including antibacterial treatment, tissue regeneration, and wound healing. The commonly used scaffolds antimicrobial fillers are antibiotics, antiseptics, peptides, ceramics, metals, and carbon-based nanomaterials. They demonstrated significant bactericidal and biocompatibility results *in vitro* and executed well for *in vivo* bone regeneration, antimicrobial, and biocompatibility results using a rabbit model. Hydrogel-based scaffolds incorporated transition metal ions or all-small-molecules to achieve significant antimicrobial activity. These prepared all-small-molecule dynamic metallogels exhibited major promising features, including conductivity, tunable mechanical properties, controlled drug release, and suppressed sepsis [37]. Moreover, these materials have been tested in tissue engineering, wound dressing, drug delivery, and cancer therapeutics [38]. In addition, scaffolds containing antimicrobial fillers have been designed to prevent and treat infections during tissue engineering, bone regeneration, and skin resurgence [39]. Meanwhile, commonly known structures for each dimensional classification are shown in Fig. 3.

2.2. Antibacterial potential of nanomaterials to combat antibiotic resistance

Various nanomaterials have been proven to be antimicrobial, which can treat multifarious infections, including multi-drug-resistant infections. Despite the continuous progress in this research field over the last two decades, employing advanced techniques in nanobiotechnology and biomedicine is highly competitive. Therefore, great efforts are required to discover new and advanced technologies that could form the foundation for antibacterial or antibiofilm treatments and would be better than the current antibiotic therapeutic ways, for which we need to understand the type of bacterial resistance and mechanisms of resistance against antibiotics that we could treat them in a better way [13,40].

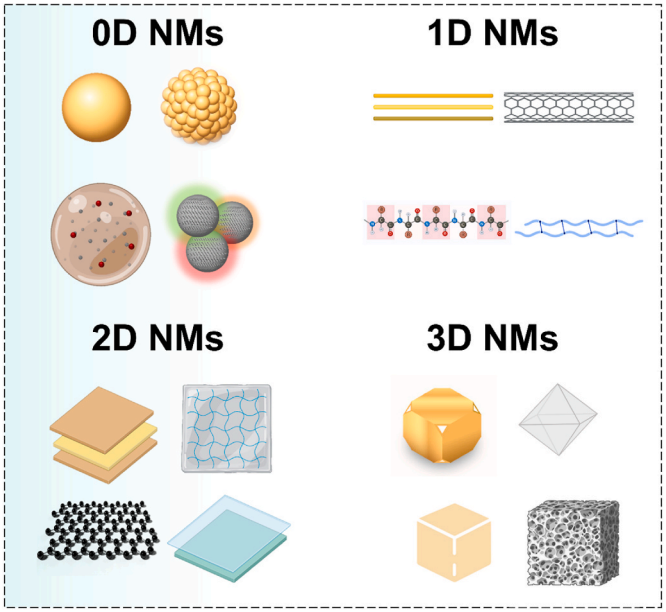

Fig. 3. Commonly known structures for 0D (spherical nanoparticle, nanocluster, silica nanoparticle containing different gases, carbon dots), 1D (nanowires, nanotube, nanorod, linear peptide, linear co-polymer), 2D (nanoplates, nanofilms, linear hydrogel with crosslinked peptides or/and polymers, graphene sheet) and 3D (nanocage, nanocube, nano-framework, commonly used cubical scaffold) nanomaterials. Created with BioRender.com.

2.2.1. Antibacterial strategies by nanomaterials

Over 400 antibacterial NMs have been reported during the past decade as nanotechnology has become one of the emerging research areas in multidisciplinary fields. However, nanobiology studies encounter low reproducibility data due to the limited standardization in nanotechnology [41]. Xie et al. analyzed many publications and selected commonly employed antibacterial mechanisms by NMs, reported widely in the literature. These antibacterial antibiotic-free treatments include metal NMs, carbon-based NMs, borides, nano-polymers, and nanocomposites [42]. Metal NPs (Ag, Au, CuO, and ZnO) display higher antibacterial efficiency than antibiotics with the lowest MICs data. Not all the NMs show similar antibacterial effectivity and display relatively low efficiency compared to antibiotics. 2D NMs such as BN nanosheets and Ag-integrated polysaccharide nanocomposites showed selective killing of bacteria with higher biocompatibility. According to molecular initiating events, six identified antibacterial mechanisms can be useful in understanding the nano-microbe interactions and their impact on the evolution of microbial resistance. These antibacterial mechanisms by NMs include ionic killing, NP aggregation-mediated cell trapping or wrapping around cells, nucleic acid arrest, catalytic killing, and destruction of cell membranes and the electron transport chain of bacterial cells. Despite the exhibition of the effective killing of bacterial cells, there is a lack of quality experimental data to convince the contributions of each interactive force to the antibacterial properties of NMs. In addition to the direct interaction of NMs, some 2D NMs (graphene and its derivatives) also assist in antibacterial killing by generating micro and nanobubbles that could induce and interrupt bacterial respiration and perforated or weakened cellular membranes [43]. Besides the antibiotic-free (NMs-based only) treatments, NMs have been combined with various macromolecules to achieve improved antibacterial activity against MRSA and delay the evolution of antibiotic resistance. Metals like Ag, Cu, Zn, and Mg have been practiced to treat diseases long before the conventional antibiotic revolution. Most of the NMs demonstrated the significance of their physicochemical properties, which can be further exploited to improve their antibacterial efficiency effectively. These properties allow them to be used in multi-model antibacterial strategies by highlighting specific physicochemical properties such as morphology, thermology, mechanical, and optical properties. Other physicochemical properties can respond to specific stimuli, including sustainable ion release or ROS generation under a certain pH range and temperature and sensitivity toward sonodynamic and acoustic strategies with better antibacterial performance [44]. Moreover, microbes, including bacteria, do not possess the universal resistance to all these metals and lack a better adaptation strategy against them. In case of failure of one antimicrobial metal, other metal-based composites and metal-based antibiotics could step in and prevent the evolution of antibiotic microbial resistance.

2.2.2. Anti-biofilm strategies by nanomaterials

There are three possible strategies to combat biofilms' resistance, including (a) surface modification technique, namely chemical modification, stimuli-responsive surfaces, or topography texturing to impede bacterial adhesion and proliferation; (b) nano-agents delivery across the biofilm layer, which may kill bacterial cells by direct interaction or by the indirect drug release, and (c) physical destruction of biofilm (EPS) *via* shear stress, interfacial tension, electric waves, cold plasma, or photothermal therapy [45]. To explain these strategies, we illustrated a scheme consisting of advanced surfaces or NMs and their significant role

after interacting with bacterial cells and biofilm, immediately causing antibacterial impact. Additionally, we showed the importance of physical methods in antibacterial and antibiofilm destruction; a detailed illustration is provided in Fig. 4. According to the second strategy, the delivery and penetration of nano-agents or small molecules across the biofilm layers modulate consortium virulence and is perceived as a promising biofilm eradication approach. However, there are critical issues that hinder the application of nano-agents in clinical operations, which include (1) insufficient information on their long-term effect, (2) properties that limit the utilization of these nano-agents in pharmacological formulations, (3) low stability, (4) limited availability, and (5) face difficulty to reach the target sites within the host cells. However, antibacterial NMs act through one or more mechanisms to kill the invading pathogens or inhibit their growth, similar to antibiotics' action [46]. In the past literature, antimicrobial mechanisms were predominantly focused on molecular aspects, which included cell damage at the molecular level, such as membrane impairment, physical disruption, and DNA and protein dysfunction. It also involves the production of ROS and regulates signal transduction [47–49].

In recent literature, antibacterial mechanisms have been classified according to their functional targets against bacterial cells. The expansion of conceptually novel bactericidal surfaces has been increasing rapidly due to the current improvements in nanofabrication methods. This physical process empowers the manipulation of surface dimensions in the nanoscale regime [48,50]. A set of assorted bactericidal nanopatterns can be employed as various types of surfaces, from soft materials (polymers to fatty acids) to tough materials (carbon, metals to alloys). Then again, the specific antibacterial mechanisms behind their bactericidal performance remain difficult to identify due to the advanced nanofabrication assemblage. However, the new physical bactericidal performance of nanopatterned surfaces has been stated, which disclosed the impact of nanoscale topography on bacterial adhesion with the least viability concerns. Moreover, antibacterial NMs have been classified as attractive tools that are intrinsically antimicrobial and used as nano-carriers for various biological applications, revealing their functional qualities. Due to their intrinsic antimicrobial activity, these NMs are alternative tools for tackling MDR biofilms and possess the capability to outwit antibiotic resistance mechanisms [47, 48,51].

2.3. Designing and fabrication of 2D nanomaterials

2.3.1. Synthesis

Past literature and current research reports have covered various topics, including nanoparticle synthesis and biological application. However, researchers can make further substantial contributions in the field of nanoscience, which has two main thrusts, i.e., NMs' synthesis and functionalization. Commonly, 2D nanomaterials are synthesized using top-down and bottom-up approaches. Both methods are briefly discussed here with a comparative explanation. In the top-down method, the bulk material is directly exfoliated into nano-sized materials by removing building blocks from the substrate or cutting the atomic crystal planes. This method covers alternative ways of exfoliation, including ion intercalation, mechanical treatment, liquid-phase, and surfactant-assisted exfoliation. By following these methods, various 2D NMs can be fabricated as single, double, or multi-layered nanosheets in various physiological solutions. Among various exfoliation methods, the liquid-phase approach is the most proficient and adaptable process that allows the synthesis of materials in large quantities, favoring their application in biomedicine [52]. Moreover, this

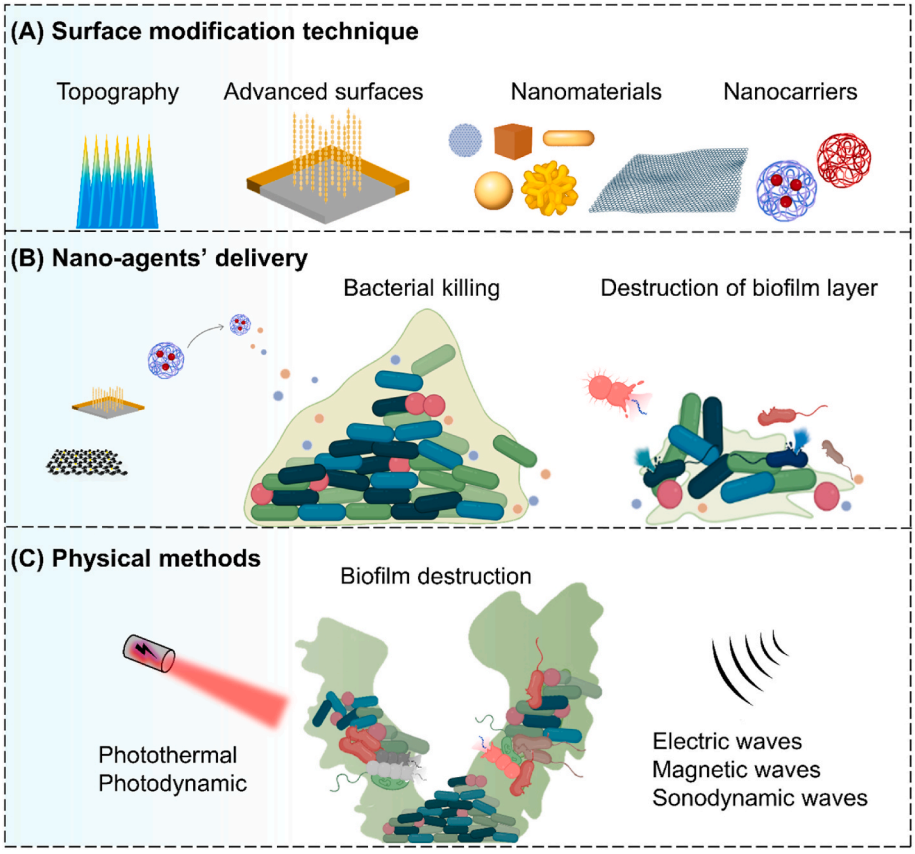

Fig. 4. Antibacterial propensity and permissive biofilm-targeting strategies *via* **(A)** Surface-modification techniques, **(B)** Bacterial killing and biofilm destruction *via* nano-agents including NPs, advanced surfaces, nanoplatform, and nanostructures containing the drug, **(C)** Physical methods for destruction of biofilm structure. Created with BioRender.com.

process can fabricate specific surface functionalization, which is exceptionally advantageous for stabilizing nanosheets in solution. Generally, these surface modifications of 2D NMs induce defects that affect their electronic properties [53]. However, these defects are prerequisites for further chemical functionalization and modulation of the material's characteristics. There are several other top-down methods to produce 2D NMs, such as mechanical milling (in which the bulk material is mechanically milled to produce separate sheets), lithography (including ion beam lithography, electron beam lithography, and photolithography), laser ablation, arc discharge method, and sputtering, have been using to produce 2D NMs [54]. In contrast, the bottom-up method fabricates layered 2D NMs *via* the regulation of supplemented atoms to the substrate for their synthesis while controlling the composition and structure of NMs [55]. This method is classified into various types, including chemical vapor deposition growth (CVD) and wet chemical synthesis. These bottom-up processes allow the synthesis of size-controlled and chemically pure NMs. However, the second approach is more versatile, while CVD is limited as it requires an appropriate substrate to fabricate the desired material under strict reaction conditions and final separation from the substrate [52]. This makes it less appropriate for biomedical applications; however, it is suitable for device fabrication to design single-crystalline 2D nanosheets. On the other hand, wet chemistry is used to synthesize layered-hydroxide-like NMs, where the controlled composition and ratio between single atoms are the ultimate factors that endow desired properties to these materials [56]. Among bottom-up methods, wet chemical approaches are extensively used to produce ultrathin materials and other nanomaterials. These approaches include hydrothermal, solvothermal, co-precipitation, and sol-gel synthesis. These approaches are considered as a practical process to produce 2D NMs due to their simplicity, cost-efficiency, and can be handled at low and moderate-to-high temperatures.

2.3.2. Prominent properties

At the nanoscale level, the physicochemical properties of metals dramatically changed from their bulk-metal counterparts due to their size. These changes to inherent fundamental properties of NMs showed expedited ion release, hardness, plasmonic, and superparamagnetic properties [49,57]. Moreover, these NMs respond differently to external stimuli in contrast to their bulk-metal counterparts, such as their response under light during photocatalytic and photothermal activity has been altered, while their response in the case of magnetically induced hyperthermia has also been changed, where the stimulus is magnetism [58–60]. In this diverse field of nanoscience, 2D NMs are the most ideal and attractive nano-systems, offering multiple property mechanisms based on (electro and photo) catalysis occurring on their surfaces where all the atoms are participating in the interaction. There are no bulk atoms on the surface, and atoms at the core of the material are inaccessible for interaction, unlike in the case of 0D and 3D NMs. 2D NMs are also different than 1D NMs in terms of electron movement, as 1D supports electron movement confined within two dimensions only. Examples of 1D NMs are nanowires, nanofilaments, nanotubes, nanorods, and nanofibers, whereas 2D NMs exhibit modifiable electron confinement systems. 2D NMs possess comparatively improved and prominent properties compared to their competitive counterparts. These properties include their high surface area, corresponding to the total effective area participating in the interaction. Their high charge carrier mobility is another fascinating feature that brands them as an extraordinary podium for catalysis and other energy transformations. 2D NMs play an important function in fast electron and ion transport owing to their thermal and electrical properties, making them more desirable and can be used in tuning other nanocomposites. For example, graphene has the highest specific area (2630 m^2/g) and exceptional carrier mobility (200,000 $cm^2\ V^{-1}\ s^{-1}$) [54]. Their extraordinary mechanical strength prevents them from collapsing, unlike in the case of some 3D NMs, which are prone to collapse and loss of structure over the time of any physical or chemical treatment. In the 2D NMs' family, MXenes showed one of the highest solution-processable materials with a measured Young's modulus of 502 GPa for Ti_3C_2. These 2D NMs are an excellent choice for constructing advanced machines with high mechanical stability by improving the mechanical properties of other nanocomposites [61]. By adding to their prominent features, their flexibility is one of their highly desired characteristics, which makes them an ideal choice for designing flexible electronics and sensors. They have already replaced conventional strain sensors in wearable electronics [62]. Moreover, their contemporary optical properties are displayed after observing an ultrathin single or few atomic layers of 2D NMs, including plasmonic effects, emission, absorption, and light sensitivity. Their unique optical properties and X-ray attenuation provide an effective approach to cancer treatment using advanced radiotherapy and phototherapy [63]. Besides the continuous growth of the 2D NMs family, their properties have not yet been fully explored. 2D NMs possess a few other astounding properties, i.e., having the capability of intercalating various species (ranging from ions to atoms and atoms to molecules) reversibly into the crystal gaps and presenting a large number of active sites that accelerate the process of surface functionalization and diverse their application areas. Each set of 2D NMs has a distinctive set of features that makes them valuable for a range of applications [54,64]; each set is explained in section 3. Other forms of NMs (including 3D NMs) are associated with some major issues that hinder their applicability in designing modern nanodevices and solving existing real-world problems. These associated issues are their limited structural stability, presented as an ongoing challenge; incapable to maintain structural integrity owing to their poor processability; poor interfacial bonding with limited functionality; adding diverse functionalities to the interior core or exterior surfaces remains a challenge halting their multifunctional properties; sometimes their unique and unknown properties lead to unexpected or unstated behaviors during their application, showing their unpredictable nature for which more research and evidence-based explanation is needed [65].

2.3.3. Lateral size

In addition to the prominent features, NMs' size and shape also influence their intrinsic properties. The lateral size of 2D NMs directly affects the surface area and impacts the efficacy of 2D NMs in controlling bacterial infections. The physical and electronic properties of 2D NMs can be finely adjusted by controlling their size and morphology, leading to quantum confinement effects as the size approaches the electron characteristic length scale. The reduction in size increases the bandgap, inducing semiconducting behavior and offering opportunities to tailor conductivity and band structure for specific applications. The optical properties of 2D NMs, including absorption and emission, can be effectively manipulated by size adjustments, impacting absorption and emission spectra and enabling precise control over the wavelength range of light absorption and emission [66]. Furthermore, variations in size also modulate the chemical reactivity of 2D NMs. Size reduction resulted in a higher density of reactive sites due to the increased proportion of edge atoms to bulk atoms. This increased surface-to-volume ratio can improve the material's reactivity toward various chemical species, making them suitable for catalytic applications. Moreover, the lateral size of 2D NMs also influences their catalytic properties, affecting the epitaxy, interface, and alignment, which are crucial for improved performance as nanozymes in theranostic applications. The lateral size of 2D NMs causes an antibacterial effect by disrupting the phospholipid membranes of bacteria. Larger-size GO and MoS_2 nanosheets exhibited stronger antibacterial activity than smaller ones [67]. The lateral size and thickness of 2D NMs also impact drug load capacity shape-dependent effects and demonstrate the importance of size optimization for increased antibacterial effects against wide-spectrum bacteria. Such as, the antibacterial activity of niobium carbide-MXene (Nb_2CT_x and Nb_4C_3Tx) sheets is influenced by their sheet size and atomic structure, depicting a correlation between lateral size, thickness,

and antibacterial properties. Size plays an imperative role in antibacterial efficacy and effectively combats antibacterial resistance [68].

2.3.4. Surface functionalization

A wide variety of 2D NMs has been investigated for their antibacterial efficacy employing different antibacterial strategies, including (1) a combination of antibiotics with 2D NMs for enhanced drug activity and controlled release, (2) coated surfaces with layered 2D NMs or (3) exploitation of inherent antibacterial capacity of 2D NM itself. In the first strategy, antibiotics can be combined with 2D NMs to offer an alternative approach to drug-resistant pathogenic bacteria. The highly effective beta-lactam antibiotic, cephalosporin, has been incorporated into LDH layers composed of zinc and aluminum, which showed an effective delivery system of the antibacterial drug molecules and inhibited *S. aureus* proliferation at a significant rate [69]. The second strategy involves novel coating materials, which offer an important platform for combating bacterial resistance. In this direction, multi-layered nanofilms have been designed and fabricated by intercalating titanium nanosheets (TNS) with a natural antibacterial agent, i.e., lysozyme (LSZ). Later on, these customized surfaces of TNS/LSZ were investigated against *Micrococcus lysodeikticus* (*M. lysodeikticus*) under UV irradiation, leading to photoactivation and high antibacterial activity enhanced cell killing. This strategy can be easily modulated further for synthesizing different nanofilms intercalating other antibacterial agents [59]. While the third antibacterial strategy represents an alternative approach to natural or synthetic antibiotics when used alongside NMs. This approach comprises 2D NMs fabricated with noble metal NPs, which are excellent electron acceptors and display enhanced ROS generation. For example, silver nanoparticles fabricated hexagonal boron nitride nanosheets (hBN-Ag) showed higher antibacterial activity than polydopamine-hBN nanosheets towards *E. coli.* and *S. aureus*. Their results showed that not only hBN-Ag nanosheets exert significant antibacterial activity, which was certainly due to the presence of AgNPs. However, h-BN nanosheets also mediated physicochemical interactions with bacterial cells that aid in the antibacterial activity of fabricated material [60]. The 2D NMs exhibit strong antibacterial properties regardless of their size and combat bacterial resistance *via* various mechanisms such as physical damage, controlled ion release, cellular toxicity, and oxidative stress. Nevertheless, we can achieve stronger antibacterial properties by tailoring their lateral size and thickness by utilizing the full potential of sheet size, thickness, orientation, and drug loading capacity to minimize antibiotic resistance.

3. Tailoring 2D nanomaterials against pathogenic bacteria

Recent innovations in nanotechnology led to the development of NMs, especially metal-based materials with antimicrobial properties. These metal-based NMs fulfill the critical need for developing new antimicrobial technologies as an alternative approach, which can work in combination with traditional antimicrobial therapies. These antimicrobial technologies must conform to a range of quintessential antimicrobial criteria to be effective. The key criteria include 1) efficient antimicrobial activity, 2) selective killing of pathogenic microorganisms, 3) facilitating clinically practical delivery methods, 4) fast acting, 5) low or zero cytotoxicity, and 6) the capability to regulate temporal and spatial delivery. Most reported metal-based NMs have already shown antimicrobial properties in both *in vitro* and *in vivo* experiments and addressed many of these criteria with varying success [70]. In the last 25 years, NM-based antibacterial agents have emerged as one of the promising advances for combating resistant bacteria. Different research groups have investigated 0D to 2D NM-based approaches worldwide and demonstrated that they could be promising alternatives for bacterial treatment [71]. Moreover, 3D hybrid NMs have extensively reduced the number of bacterial cells by up to 100 % of the killing rate against pathogenic *E. coli*, *P. aeruginosa*, and *S. aureus* [49]. However, 3D NMs will not be discussed in this review. In addition, 0D plasmonic nanomaterials like silver nanoparticles have already shown higher antibacterial activity against antibiotic-resistant bacteria. It is well-documented that metal NPs combat bacterial resistance *via* different antibacterial strategies [58]. Recent reports indicated that these NM-based antibacterial agents could act as efflux pump inhibitors [72], which is one of the main reasons behind antibiotic resistance among bacteria. Due to the facts mentioned above, NMs are less likely to induce bacterial resistance than antibiotics available in the market [73]. Due to their significant antibacterial capability, scientists hope these NM-based antibacterial platforms will offer new, effective ways to treat bacterial infections [74]. By modulating these unique properties of metal-based nanomaterials, researchers may transform pilot-scale research into a widely applicable use of nanomaterials, from next-generation electronics to numerous practices in biomedicine.

3.1. Modulation of 2D Nanomaterial's physiochemical properties

Recently, many research studies have been done on exploiting bactericidal applications of 2D NMs. Carbon-based 2D NMs have attracted much attention due to their relatively higher biosafety and exceptional physicochemical properties. In this section, we will discuss the bactericidal propensities of carbon and nitride-based NMs (graphene, graphene derivatives, graphitic carbon nitride, boron nitride), metal-based NMs (transition-metal dichalcogenides/oxides (TMDs/Os)), and a few other exceptional NMs (MXenes, bismuth, BP, borophene).

3.1.1. Carbon and nitride-based nanomaterials

Different allotropes of carbon have been configured to generate a variety of carbon-based nanomaterials, which include fullerene (0D), carbon dots, carbon nanotubes (1D), graphene (2D), and its derivatives. Being a main part of the 2D network of sp^2 hybridized carbon atoms arranged into single atomic layered sheets, graphene is the basic component for graphitic materials of all other dimensionalities that can be wrapped into 0D fullerenes, rolled into 1D carbon nanotubes and stacked up to configure a multilayered 2D sheets of carbon or 3D graphite [75]. This section is divided into two major parts, i.e., carbon-based 2D NMs (graphene, g-C_3N_4) and nitride-based 2D NMs (g-C_3N_4, h-BN) as g-C_3N_4 and h-BN exhibit interesting structural analogies with graphite. In the same manner, boron nitride (BN) contains an identical number of boron and nitrogen atoms, i.e., isostructural to graphite; on the other hand, the nitrogen and boron atoms show sp^2 hybridization to form a strong σ bond, whereas, carbon atoms of graphite (or graphitic materials) form a π bond.

3.1.1.1. Graphene and its derivatives. Pristine graphene (PG), graphene derivatives: graphene oxide (GO), reduced GO (rGO), and functionalized graphene are the three major forms of graphene-based materials that have been exploited for antibacterial treatments. Among all carbon-based NMs, graphene nanosheets have been widely applied in disinfection due to their desirable traits, such as large surface area, relatively lower cytotoxicity, water dispersity, and electrical conductivity, which can be modified to achieve the intended biological functions. However, the purified GO materials did not impact bacterial growth as compared to the fabricated graphene-oxide (such as rGO) materials; even so, the fabricated rGO material exhibited lower antibacterial performance with higher cytotoxicity due to the changes in their physicochemical traits [76]. So far, considerable advancements have been made to advance the antibacterial proficiency of graphene nanosheets. The supramolecular carbohydrate-functionalized graphene nanosheets were fabricated with multivalent effects of sugar ligands, which showed significant bacterial killing *via* surface adherence to bacterial cells. Moreover, the antibacterial activity of GO can be enhanced by extracting lipid molecules from the cell membrane onto the surface of GO nanosheets after the dispersion interactions between lipid tails of the bacterial membrane and

hydrophobic domains of GO nanosheets [77]. This can also explain the improved biocompatible nature of coated GO nanosheets, with reduced antibacterial and cytotoxic tendencies while screening their hydrophobic domains. Generally speaking, GO nanosheets utilize dual-synergistic antibacterial approaches to achieve a desirable outcome; however, their poor stability under aqueous conditions limits their biomedical application, particularly in the antimicrobial field [78]. That is why an improved stabilization system must assess its full antimicrobial potential. In this regard, GO nanosheets were functionalized with hydrophilic polymers (polyethylene glycol-modified carboxylated GO) and used as nanocarriers for antibacterial AgNPs and sulfadiazine (SD). This hybrid antibacterial system (HAS) was constructed *via* a microwave-assisted green approach. The triple-synergistic antibacterial system showed three times higher bactericidal activity than the system lacking SD. The attributed antibacterial performance of HAS was due to the bacterial capping by GO sheets, membrane puncturing by AgNPs, and inhibitory effects of SD. A novel hybrid system is shown in Fig. 5, providing the essential details from designing the antibiosis system with their multi-functional attributes, which broaden the ultimate biomedical applications [79].

In addition to the combined antibacterial therapy, the PG is also known for demonstrating their variable antibacterial efficiency towards MDR Gram-negative and Gram-positive bacteria with the help of their high density of edges, which is the main parameter for the interaction between graphene nanosheets and bacterial cell membranes [80]. GO nanosheets have been used to kill MDR hospital superbugs cultivated on agar-based nutrient plates containing human serum to determine their cytotoxicity and genotoxicity. They showed higher bacterial growth inhibition with and without combining with antibiotics [81]. In conclusion, graphene-based 2D NMs with hierarchical nanostructures are the prerequisite to achieving antibacterial performance by bacterial adhesion and diffusion. Moreover, these conductive nanostructures are responsible for quick charge transfer across the bacterial biofilm, which could show promising antibiofilm properties. Synthetic methods and surface-functionalization will broaden graphene-based materials' design and application scope.

3.1.1.2. Graphitic carbon nitride nanomaterials. Graphitic carbon nitride (g-C_3N_4) NMs are the emerging carbon and nitride-based semiconductor materials with multiple ultrastructures and narrow bandgap, which have anticipated great attention in antibacterial research owing to their proficient photocatalytic property, larger surface area, chemical and thermal stability with an adjustable π electron conjugation system in its 2D network structure [82]. G-C_3N_4 is a metal-free polymer with a graphene-like configuration in which both carbon and nitrogen atoms are sp^2 hybridized to form aromatic six-membered heterocycles, making them a great substitute for graphite NMs [83]. In addition, extremely thin 2D g-C_3N_4 nanosheets extensively reduce the migration distance of photogenerated e^- and induce immediate catalytically active sites. Although their photocatalytic efficiency can be limited due to the fast recombination rate of photogenerated e^-/h^+ pairs (with low molar extinction coefficient) in the visible-light range, methods for increasing photocatalytic efficiency remain highly desirable. The most applied synthetic technique for pristine g-C_3N_4 is bulk exfoliation, which is associated with crystal imperfections. Due to this, researchers applied the method of introducing heterojunction to control the defects of pristine g-C_3N_4 [84]. The antibacterial application of 2D g-C_3N_4 nanosheets was investigated for the very first time when Wang et al. designed a customized graphene-based metal-free photocatalyst g-C_3N_4 wrapped with elemental sulfur for bacterial irradiation under visible light, which further strengthened their synthesis to offer better comprehensive properties [85]. 2D NMs have been exploited widely in nanomedicine and nanobiotechnology to construct advanced photocatalysts due to their chemical properties and high anisotropy. Among them, nanosheets of g-C_3N_4 have been manipulated and loaded with various elements to exhibit 100 % antibacterial photocatalytic activities. For the same

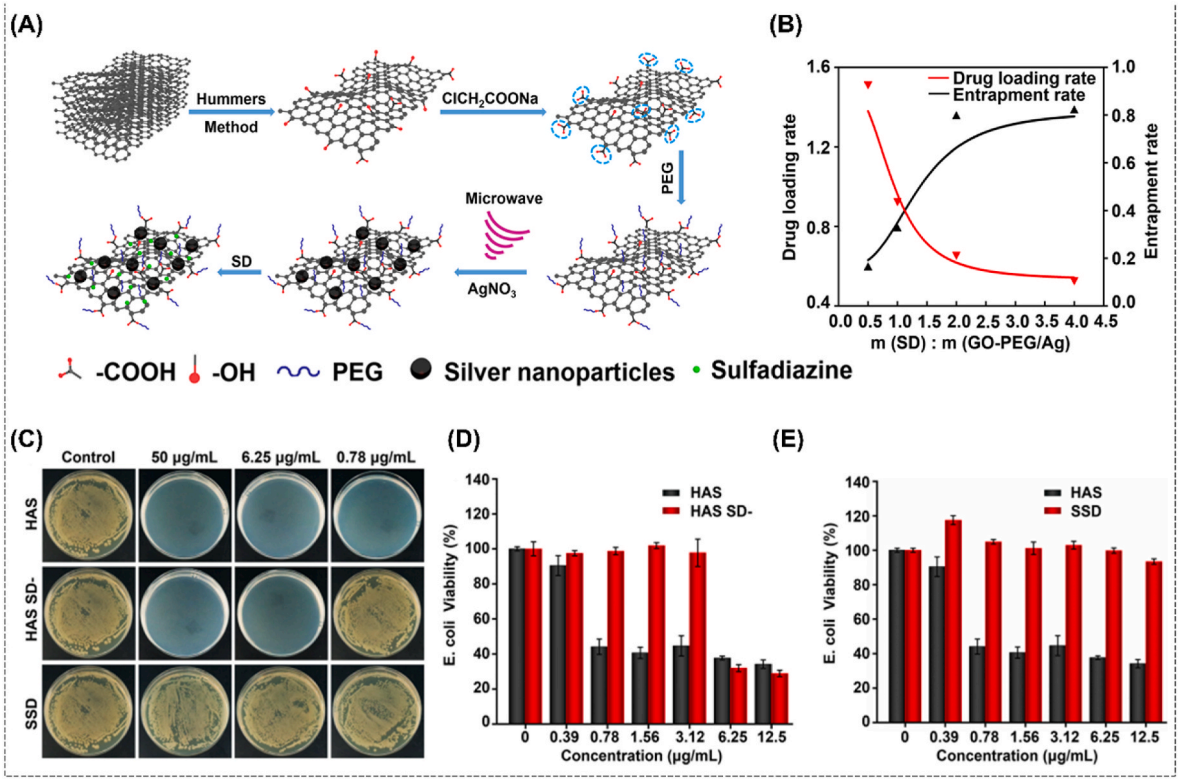

Fig. 5. Designing of antibiosis systems: **(A)** Fabrication of hybrid antibacterial system (HAS), **(B)** Drug loading capacity and entrapment rate of HAS, **(C)** Digital images of *E. coli* treated under HAS, Bacterial cellular viability of *E. coli* after treating with **(D)** HAS and HAS SD-, and **(E)** HAS and SSD. Reproduced with permission [79]. Copyright © 2020, Springer Nature.

reason, bismuth (Bi) nanospheres loaded with g-C_3N_4 were prepared, which displayed effective photogenerated charge separation and transfer efficiency compared to their pristine counterparts. Moreover, the SPR effect of bismuth caused enhanced visible light absorption that resulted in significant photocatalytic antibacterial activity with a killing efficiency of 96.4 % against *E. coli* [86]. Similarly, a bactericidal photocatalyst (Ag/polydopamine/g-C_3N_4) with accelerated antibacterial performance and superstability using the *in-situ* reduction method was designed to achieve improved photocatalytic activity by incorporating AgNPs and polydopamine under visible-light irradiation. This strategy demonstrated a synergistic antibacterial treatment by ROS generation and accelerated Ag^+ release. Simultaneously, this photocatalyst exhibited effective antibacterial activity towards *E. coli* and showed commendable biocompatibility because of the integrated polydopamine into the nanocomposite as spontaneous antibacterial killing. The plausible antibacterial mechanism and fabrication process for Ag-loaded g-C_3N_4 nanosheets is shown in Fig. 6 [87].

Generally speaking, C_3N_4-based photocatalysts have received much attention because of their various advantages in the biomedical field, although their photocatalytic proficiency is relatively lower to fulfill the needs of practical applications. More studies have been carried out to remove their practical limitations for the synthesis and customized

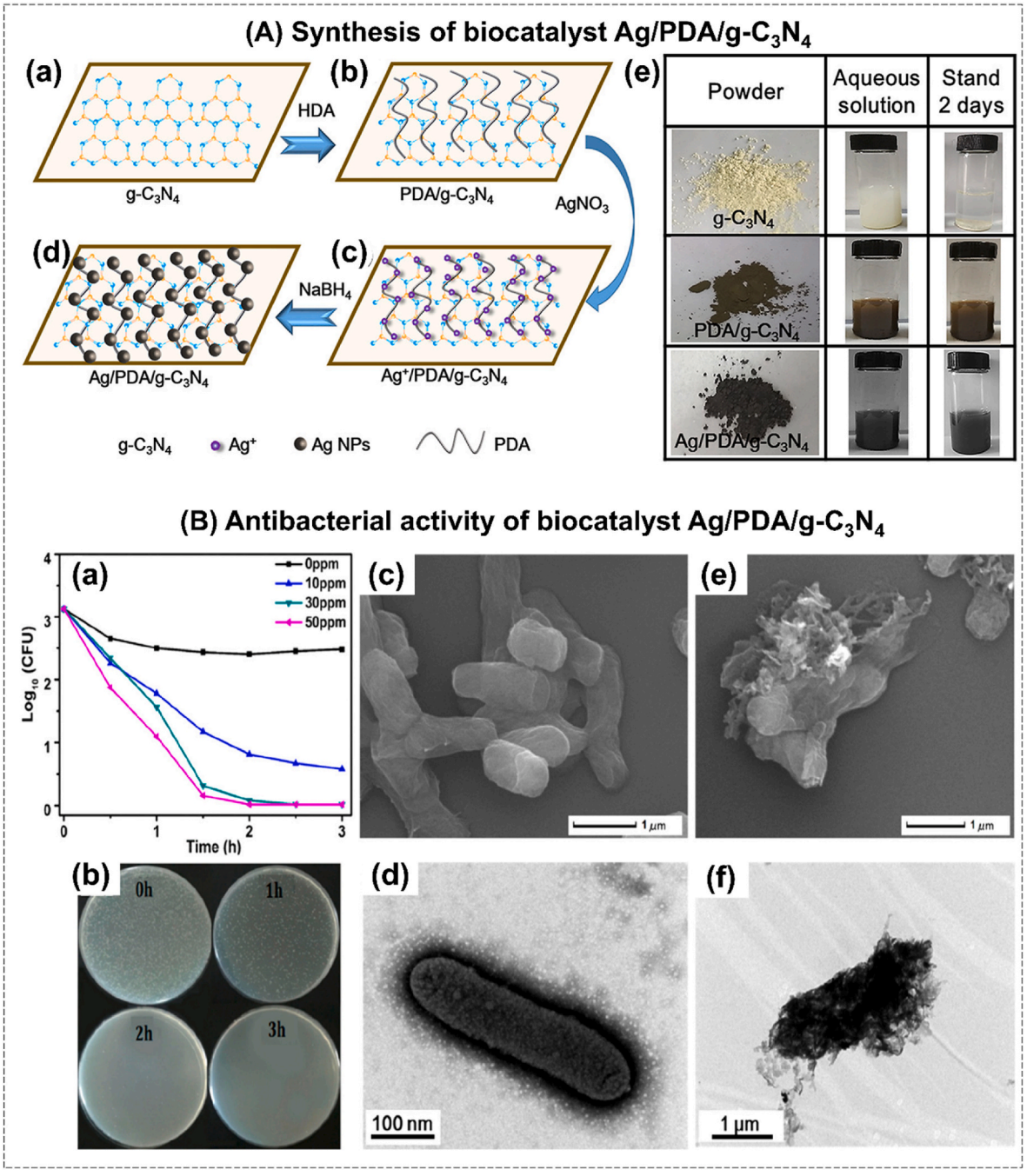

Fig. 6. **(A)** Boosted antibacterial photocatalytic performance of g-C_3N_4 NMs: (a–d) A diagram for the preparation of PDA-modified Ag-loaded g-C_3N_4 nanosheets *via* the thermal and chemical method, (e) Digital photographs of PDA modified Ag-loaded g-C_3N_4 nanosheets in powdered and aqueous solutions, **(B)** Bactericidal nature of Ag/PDA/g-C_3N_4 bio-photocatalysts: (a–b) Antibacterial effect Ag/PDA/g-C_3N_4 at different concentrations after 0, 1, 2, and 3 h, and morphological damages are exhibited in SEM and TEM images of *E. coli* cells before (c, d) and after treatment (e, f) using 30 ppm of Ag/PDA/g-C_3N_4 for 2 h under visible-light source. Reproduced with permission [86]. Copyright © 2018, American Chemical Society.

antibacterial approach of g-C_3N_4-based 2D nanomaterials. Further studies revealed better bactericidal strategies could significantly eliminate *E. coli* K-12 in water samples under visible light treatment [88]. Therefore, their light-dependent catalytic bactericidal efficiency is expected to improve. Future investigations could focus on developing synthetic methods that use various precursors and customized antibacterial strategies.

3.1.1.3. Boron nitride (h-BN) nanomaterials. In addition to the nitride-based 2D NMs, boron nitride (BN) NMs have also been used as bactericidal reagents. BN-based NMs are present in three different crystalline structures: amorphous (a-BN), cubic (c-BN), and hexagonal (h-BN) [89]. Among these BN NMs, h-BN has been investigated systematically. It is an atomic-thick 2D material with a similar crystal structure to graphene. Moreover, h-BN possesses various advantages, such as a large band gap and extraordinary chemical and thermal stability [90]. Synthetic methods for BN nanosheets have been established, such as chemical vapor deposition and chemical and thermal exfoliation. The h-BN is a great building scaffold, owing to the sp^2 hybridization nature of carbon. In addition to that point, the edges of h-BN are endowed with higher chemical activity and reduced binding energy, which makes them excellent opportunists for various materials' functions [90–92]. While the antibacterial studies on h-BN NMs are in the initial stages, they have already proved their bactericidal effect against resistant bacterial communities, when applied alone and in combined therapy. Likewise, h-BN nanosheets endowed with AgNPs using one-pot synthesis with microwave assistance were fabricated which shaped the uniform growth of NPs with proficient antibacterial activity [92]. Moreover, a facile antibacterial and antibiofilm strategy demonstrated the controlled extrusion of low-density polyethylene (LDPE) polymer matrix-embedded BN nanoflakes, exhibiting a significant reduction in several viable bacterial cells when evaluated against *S. epidermidis*, *E. coli*, *S. aureus*, and *P. aeruginosa* [93].

At the same time, the interaction of h-BN nanosheets with bacterial cells exhibited their toxicity in cellular envelopes (outer and inner membranes of bacteria) by damaging cellular integrity *via* lipid extraction, which might agree with hydrophobic cellular interaction and free-energy calculations [95]. To solve modern world problems, novel fibrous membranes loaded with h-BN and polypropylene (PP) materials have been added to the ultrathin layers of surgical face masks to promote contact killing of pathogenic microorganisms without releasing any unfavorable biocides. This antibacterial QAC-functionalized h-BN and polypropylene-loaded fibrous membranes displayed a killing efficiency of more than 99 % and 96 % against *S. aureus* and *E. coli*; a detailed antibacterial strategy is shown in Fig. 7 [94]. By understanding their synthetic mechanisms and dispersion functionalities, researchers can use various surfactants to explain h-BN nanosheets as antibacterial materials. It is worth establishing novel synthesis methods for BN

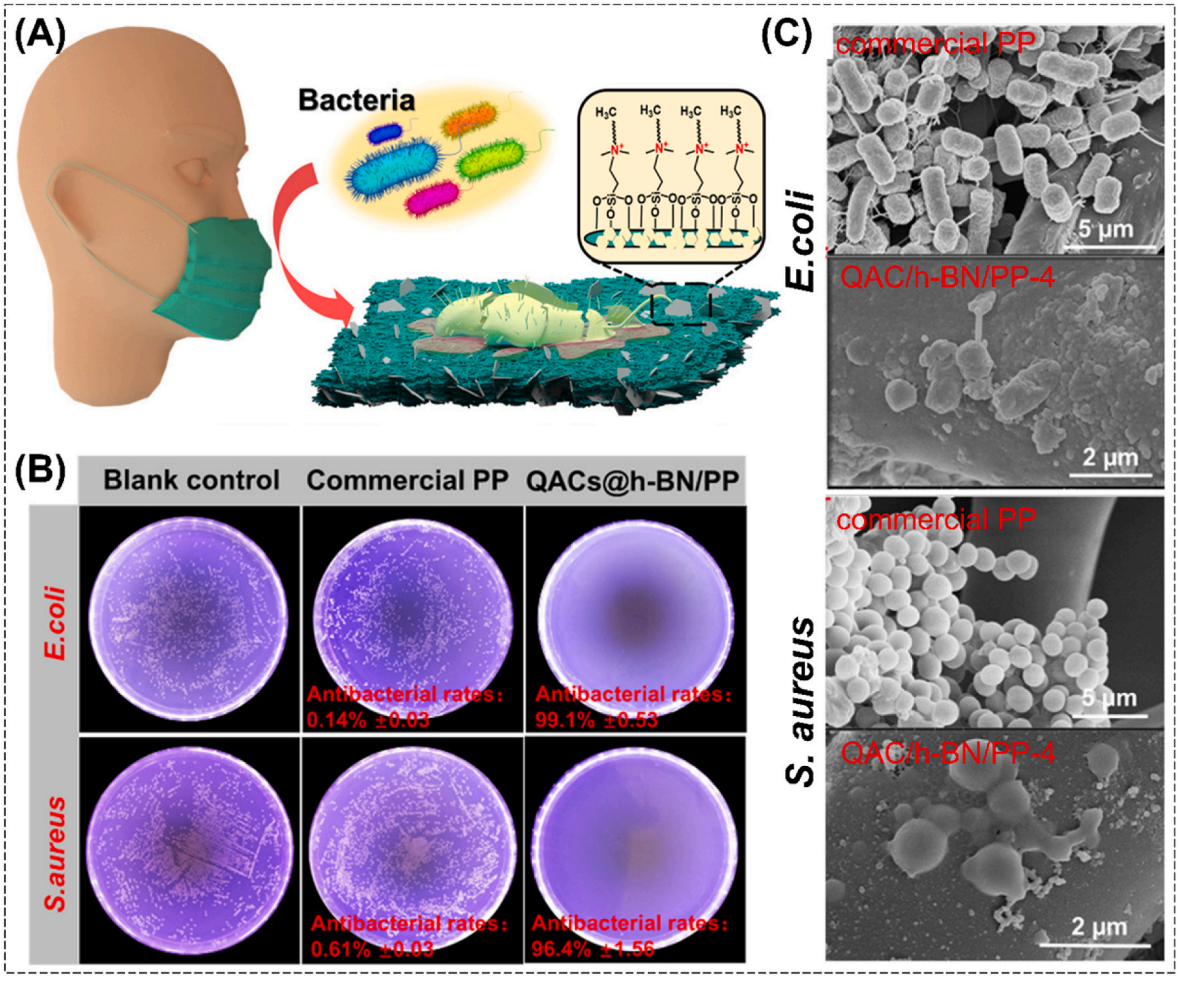

Fig. 7. Antibacterial h-BN/Polypropylene nanocomposite fibrous membranes replacing commercial face masks: **(A)** Antibacterial mechanistic of QAC/h-BN/PP nanocomposite integrated fibrous masks, **(B)** Images of antibacterial activity of commercial PP nonwovens, and QAC/h-BN/PP-4 nanocomposite integrated fibrous membranes against *E. coli* and *S. aureus via* colony-forming method, **(C)** Distingusigble SEM images of *E. coli* and *S. aureus* cells on the surface of commercial PP nonwovens and QAC/h-BN/PP-4 nanocomposite integrated fibrous membranes exhibiting a significant reduction in bacterial cell viability with prominent cellular damages. Reproduced with permission [94]. Copyright © 2021, American Chemical Society.

materials to conduct more in-depth antibacterial investigations that may also propose new insights into the molecular cytotoxicity of BN materials.

3.1.2. Metal-based nanomaterials

Metal-based NPs have been investigated as nanomedicine, nanocarriers, and antibacterial agents. However, their bactericidal efficiency is compromised due to their smaller specific surface area with fewer surface-active sites. Therefore, to achieve a high-performance bactericidal effect, these NPs were transformed into 2D metal nanosheets or decorated on the surface of 2D nanosheets to overcome such shortcomings [96]. In this direction, a synergetic bactericidal effect of photothermal therapy and Pd@Ag nanosheets was demonstrated under the irradiation of NIR light. These Pd@Ag nanosheets exhibited excellent photothermal conversion efficiency, producing heat for bacterial killing and destroying bacterial membranes *via* released Ag^{+} under NIR irradiation [97]. Lately, antibacterial metal-based 2D oxides, such as TiO_2, CuO, and ZnO, have drawn widespread attention and aided in combating resistant bacterial communities due to their strong oxidizing and photocatalytic properties. Among these metal-oxide NMs, ultra-thin TiO_2 nanosheets exhibited excellent bactericidal effects, attributed to one of their numerous advantages, including moderate stability, low cost, lower toxicity, and robust oxidizing properties with enzyme-like activity. Generally, TiO_2 nanosheets retain a three-phase structure i.e., brookite, rutile, and anatase among which anatase TiO_2 nanosheets have been widely used as a photocatalyst [96,98].

3.1.2.1. Metal-based 2D transition metal dichalcogenides. In recent times, TMDs have drawn great attention and have become principal building blocks for sensors, electronic, solar cells, and photothermal-based cancer therapy systems due to their versatile chemistry, which offers diverse opportunities [99]. Generally, TMDs consist of three atomic layers of transition metal sheets sandwiched between two chalcogen layers, giving them complicated imperfections compared to the simple monovacancy in graphene sheets. The TMDs' synthetic methods are well-established for producing high-quality nanostructures *via* the CVD method and chemical exfoliation. Multiple exfoliation methods involve liquid-phase exfoliation in a suitable solvent or surfactant and through basal-plane functionalization *via* chemical exfoliation [100]. Few other facile and high-yielding exfoliation methods were proposed for WX_2 (X = S, Se), which involved single-stranded DNA to avoid aggregation and increase their exfoliation efficiency [101]. Meanwhile, the bactericidal properties of TMDs were explored, and the 2D planar nanostructured ce-MoS_2 exhibited improved antibacterial activity due to their larger surface area and desirable electronic properties, which ensured effective physical contact with the bacterial cells [102]. Moreover, another synergetic approach opted for bacterial elimination of ampicillin-resistant *E. coli* and *E. faecalis* (*in vivo*) using a biocompatible

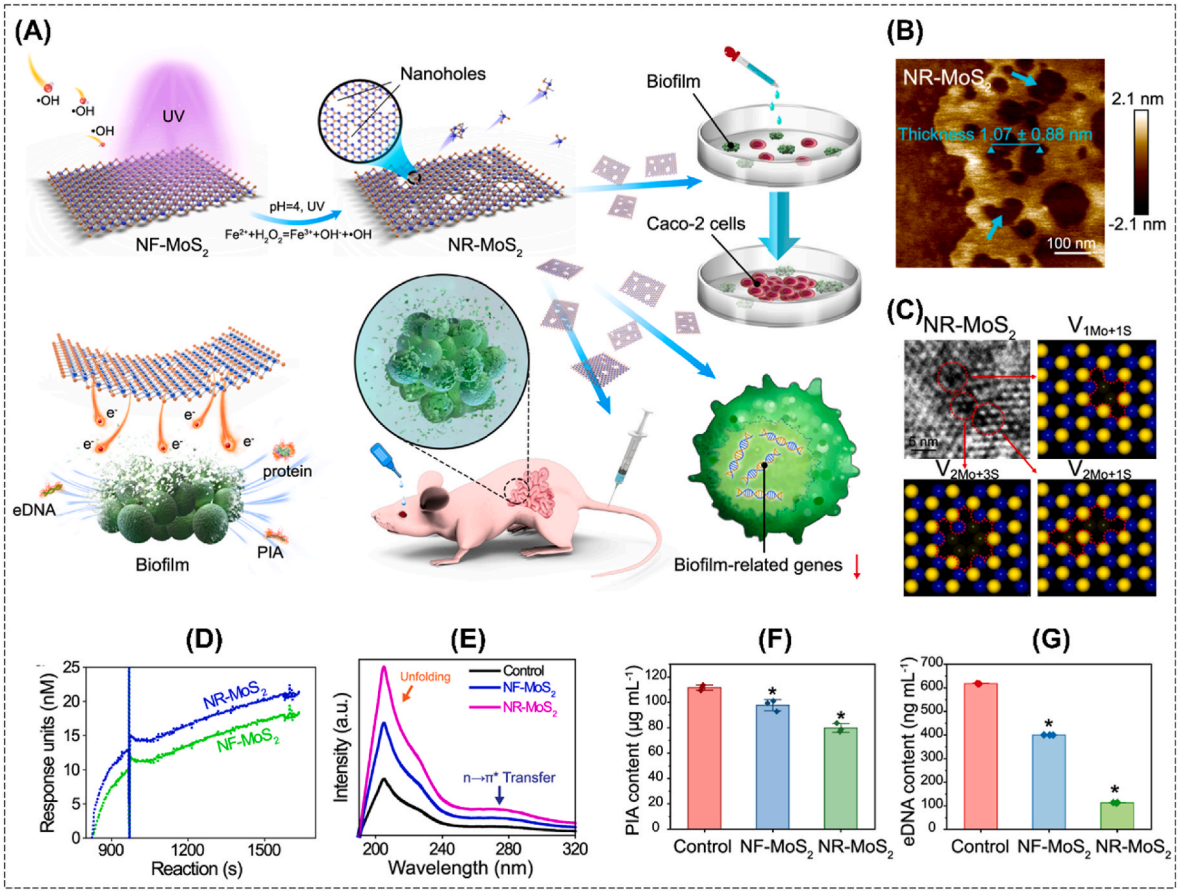

Fig. 8. Nanohole-enriched electron transport between MoS_2 and bacteria: **(A)** Illustration of nanohole-enriched MoS_2 NSs proposing anti-biofilm and anti-infection mechanisms, **(B-C)** Typical atomic force microscopy (AFM) and high-resolution transmission electron microscopy (HR-TEM) images suggesting NR-MoS_2 fabrication and exhibiting simulations of atomic vacancies of Mo and S, **(D)** SPR spectra indicating higher affinity between nano-enriched (NR-MoS_2) and biofilm than nanohole-free (NF-MoS_2) and can be used as a biosensor for detecting active compounds in biofilm, **(E)** UV–vis absorption spectra of biofilm treated with NR-MoS_2 and NF-MoS_2 respectively indicating reduction in the helication and unfolding of the protein skeleton of biofilm compounds due to active electron transport, **(F-G)** Measurement of polysaccharide intercellular adhesin (PIA) and eDNA contents of the biofilm as their main active compounds exhibiting significant reduction in PIA biomass and eDNA contents targeted by electron transport confirming anti-biofilm activity of NR-MoS_2. Reproduced with permission [104]. Copyright © 2021, Springer Nature.

808 nm laser-mediated NO-releasing MoS_2-BNN6 nanocarriers with significant germicidal activity and also supported wound healing in infected mice [103]. Such a series of studies did not stop, and one of the most recent works introduced 2D MoS2 nanosheets based on an anti-biofilm nanoholes-boosted system that inhibited *S. aureus* biofilm growth and *in vivo* infection. This study overlaid the electrochemical behavior of nanohole-enriched MoS_2 (NR-MoS_2) nanosheets and confirmed their electron transport and redox reaction by biofilm studies. In short, this behavior was responsible for efficiently annihilating major cellular components (including proteins, biofilm-associated EPS, and extracellular nucleoids) of biofilms and significantly down-regulated expression of various genes associated with biofilm formation under physiological conditions. In addition, NR-MoS_2 nanosheets efficaciously treated *S. aureus* intestinal infection, ocular swelling, and corneitis; a detailed introductory scheme for preparation of NR-MoS_2 and their bactericidal activities *in vivo* with anti-infection properties is given in Fig. 8 [104]. Besides corneitis and intestinal infections, these modified bioactive materials treat infected wounds, periodontitis, and osteomyelitis by modulating cellular behavior and promoting wound healing, soft tissue regeneration, and bone tissue recovery [105].

3.1.2.2. MXenes. Recently, a new family of 2D NMs comprising transition-metal carbides and carbonatites has gained much attention in biomedicine [106]. MXenes displayed many desirable attributes that meet the requirement of an effective antimicrobial agent, such as their hydrophilic nature derived from functional groups of oxygen, hydroxyl, or fluorine, large specific surface, high conductivity, easy functionalization, and strong absorption in the NIR region [107]. In addition, these materials are biocompatible and degradable, which can be removed from the mice's body owing to their key elements (carbon, nitrogen) and the inertness of transition metals (Ti, Nb, Ta) to living organisms [108]. Furthermore, multifunctional 2D nanosheets of MXene@PDA provide an efficient antibacterial strategy against methicillin-resistant *S. aureus* (MRSA)-infected wound healing and skin regeneration. This material has overcome two major problems of antibiotic resistance and delayed wound repair without the aid of broad-spectrum antibiotics and bioactive molecules [109]. There are multiple emerging modes of antibacterial MXenes (niobium carbide MXene with titanium plate), which are capable of destroying bacterial biofilms *via* downregulating energy metabolism pathways, inhibiting biofilm formation, and promoting biofilm detachment *via* accessory gene regulators such as *Agr*. Moreover, these 2D materials control bacterial eradication, mitigate the tissue regeneration process *in vivo*, and alleviate proinflammatory responses *via* ROS generation, promoting angiogenesis and tissue remodeling. An illustration of the fabrication of niobium carbide (Nb_2C) MXene titanium plate (2D Nb_2C@TP NMs) with their respective antibacterial and antibiofilm capabilities, is shown in Fig. 9 with the potential to manage multimodal infection [110].

In addition, MXene@silk multifunctional fabric was fabricated with exceptional photothermal and electrothermal dual energy conversion performances, which exhibited outstanding antibacterial activity against *E. coli* with a killing rate of 99.55 % under 20 min. The facile synthesis of antibacterial medical fabric has become the trend due to its uniquely designed robust coating and chemically and thermally stable properties. Moreover, the facile assembly of $Ti_3C_2T_x$ MXene flakes packed on the surface of polypropylene (PP) fibers has already demonstrated an *in vitro* antibacterial study that reduced bacterial viability up to 100 %, instigating physical membrane damage and light-induced ROS

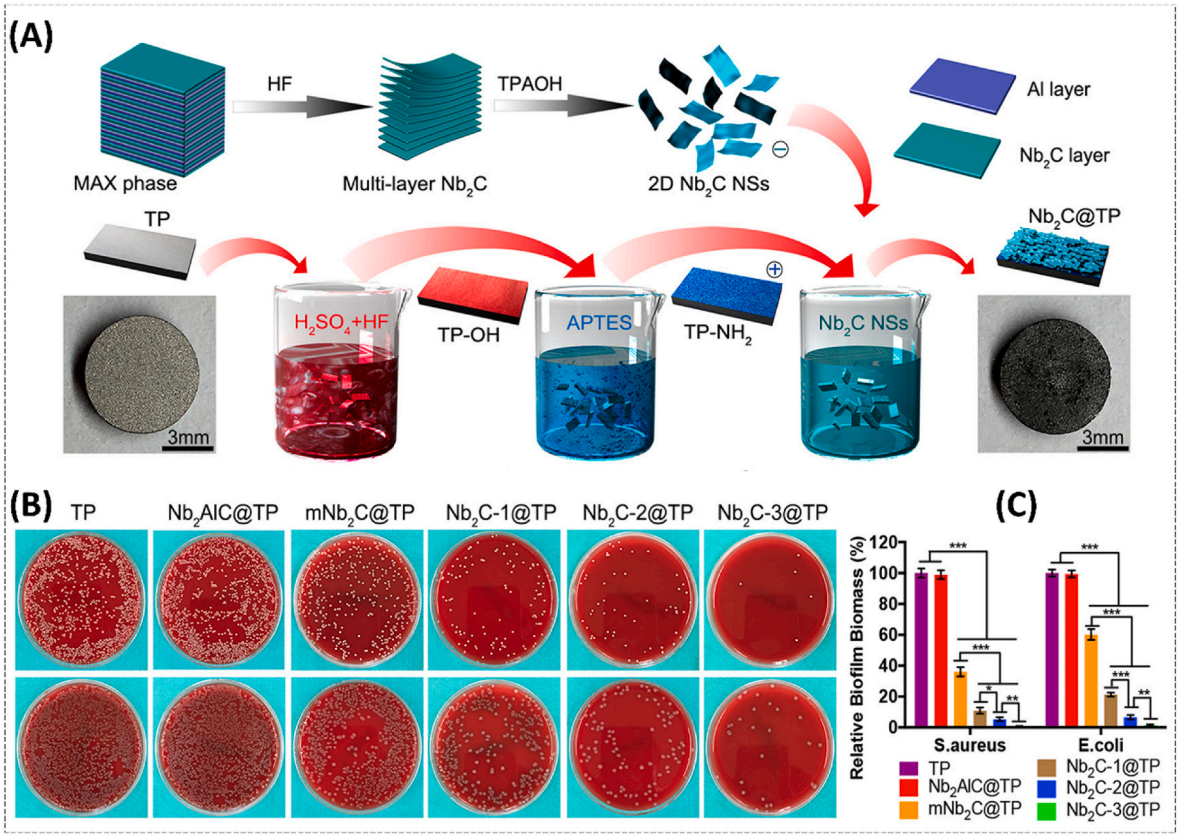

Fig. 9. Multimodal antibacterial activity of MXene titanium plate (NTP)-based thermotherapy: **(A)** Schematic diagram for fabrication of 2D niobium carbide (Nb_2C) MXene titanium plate i.e., Nb_2C@TP, **(B)** Typical images of bacterial colonies from biofilms on culture plates showing significant reduction in several bacterial colonies, **(C)** Reduction in relative amounts of corresponding biofilm biomass. Reproduced with permission [110]. Copyright © 2021, American Chemical Society. Used **Nb_2C@TP** NMs in this study were classified as Nb_2AlC@TP, multilayered Nb_2C@TP (derived from bulk Nb_2AlC and multilayered Nb_2C respectively), Nb_2C-1@TP, Nb_2C-$_2$@TP, and Nb2C-3@TP (prepared from Nb_2C NSs at varying concentrations (1.0, 1.5, and 2.0 mg mL^{-1}) with TPs-NH_2) respectively.

generation [111]. This category of 2D NMs has been showing consistent improvements to achieve advanced practical results. Nevertheless, further advancements into the antibacterial field of other MXenes with different transition metals or surface terminations remain to be investigated.

3.1.3. Other examples of 2D nanomaterials

3.1.3.1. Bismuth-based nanomaterials. Bismuth (Bi)-containing nanomaterials have been studied extensively in biomedicine as an active ingredient in treating *Helicobacter pylori*-associated gastrointestinal infections. Due to their physicochemical and optical properties with cost-effective fabrication processes, Bi-based NMs can be used to construct various nanostructures that possess unique structural and compositional features offering favorably enhanced near-infrared (NIR) absorbance, high X-ray attenuation, and exceptional light-to-heat conversion efficiency with a longer circulation half-life as these qualities are highly desirable in research areas of antibacterial, bioimaging, anti-tumor, and other medical therapeutics [112]. The global rise of MDR bacteria has caused a plethora of difficult-to-treat illnesses and serious threats to human health. Bi-based NMs are highly responsive to the NIR absorbance that instigated an enhanced antibacterial activity against MDR bacteria and helped to achieve up to 99.6 % and 99.2 % antibacterial efficiency against *E. coli* and methicillin-resistant *S. aureus* [113]. In addition to their excellent antibacterial properties, Bi nanocomposites of zinc cyanide (CN-Zn/Bi_2S_3 nanosheets) can also regulate genes responsible for tissue regeneration and wound healing *in vivo* [114]. Most phototherapeutic agents can be removed easily from the organisms due to their fast clearance from the system *via* reticuloendothelial or phagocytosis. Bi-based NMs can easily camouflage as autologous compounds within the body to dodge immune response and prevent immune clearance [115]. Moreover, macrophages loaded with Bi_2Se_3 nanosheets showed longer blood circulation than the nanosheets to deliver other NMs or drugs as they can circumvent the drug delivery barrier, effectively target the tumor source, and ultimately increase the effectiveness of photothermal cancer therapy [116]. Hence, this suggests a promising approach to eradicate the problems associated with MDR bacterial infections by introducing NIR-responsive Bi-containing NMs, which facilitates their biological applications.

3.1.3.2. Black phosphorus. Black phosphorus (BP), also known as phosphene, is another emerging member of the 2D NMs and has gained great attention since 2014. These BP nanosheets possess exceptional properties such as biodegradability, layer-dependent bandgap, electrical and thermal capacities, and weakened Van der Waals forces that allow their affluent exfoliation into 2D nanosheets [117,118]. BP possesses strong light absorption across the entire visible range due to its metal-free semi-conductor nature and thickness-dependent bandgap [119]. Usually, 2D NMs exhibit antibacterial effects by perturbing bacterial cell wall architecture and causing leakage of cytoplasm and cell membrane dysfunction, known as the nanoknife effect. This effect is also observed in the case of 2D BP NMs due to their large folded surfaces and crystal lattice structure, which favor sufficient contact with bacterial surfaces. Upon interacting with bacterial cells, 2D BP NMs mainly disrupt the bacterial membrane lipid bilayer and extract many phospholipid molecules from the membranes [120]. A similar antibacterial effect was observed in *E. coli* and *B. subtilis* using BP NMs, further confirmed under dark conditions [121]. Moreover, BP has been used in photothermal and photodynamic antibacterial applications, generating singlet molecular oxygen ($^1O_2$) under visible light irradiation [120]. Besides brilliant photo-induced bactericidal efficiency, the photosensitized BP is also suitable for disinfection or sterilization. They exhibit qualities like broad-spectrum microbicidal activity against MDR bacteria and wound healing [120,122]. Ouyang et al. fabricated an artificial skin specified as BPN@gel by suspending BP NMs in a matrix gel containing fibrinogen and gelatinase that demonstrated an excellent photothermal bactericidal effect on the wounds of diabetic mice [123]. In addition, BP-embedded chitosan hydrogels (CS-BP) were constructed *via* electrostatic interactions, which initiated visible light-driven photodynamic antibacterial activity and alleviated wound healing [124].

3.1.3.3. Borophene. With the increasing demand of global interest in the fabrication of 2D NMs, a new group of emerging materials containing boron has attracted distinct attention alongside graphene, h-BN, and MXenes, known as borophene. As mentioned above, scientists fabricated intricate sets of 2D nanosheets using boron-based nanomaterials with higher antibacterial performance. Borophene is an exciting new entry to the class of 2D NMs, which have been at the forefront of extensive research studies. They possess uniquely varied electronic, chemical, and optical properties in their polymorphic forms, with different band gaps. Recently, Tasaltin et al. designed borophene nanosheets intercalated with β-rhombohedral crystalline nanostructures, which exhibited significant antibacterial effects against MDR bacteria, including *S. aureus*, *P. aeruginosa*, *E. coli*, and a few other total aerobic mesophilic microorganisms. These multifunctional nanosheets also demonstrated noteworthy antifungal properties against *Aspergillus brasilliensis* and *Candida albicans*. These advanced modified nanosheets will play an important role not only in biomedicine and disinfection but also in disinfection. However, due to their biocompatibility and exotic nature, they could also be the leading materials for cosmetic applications [125]. In addition to the fabrication of new crystalline antibacterial nanostructures, ultra-thin and large borophene nanosheets can be designed with different biopolymers such as biocompatible polydopamine (PDA) and transformed into smart delivery nanoplatforms, which can effectively target cellular system in the tumor environment due to the enhanced cellular uptake efficiency [126]. Besides offering antibacterial and antitumor treatments, borophene can harvest the power of light and provide better solutions to handle interventional therapy in internal organs *via* fiber-optic delivery, surgeries during ophthalmological procedures, and cure cutaneous disorders.

There are a few other new members of the 2D NMs family, such as layered double hydroxides (LDHs), laponite (Lap), III2-VI3 compounds (In_2Se_3, Bi_2Se_3, Sb_2Se_3), and ruthenium (IV) oxide (RuO_2), have been considered as efficient antibacterial tools [127,128]. Moreover, fabricated laponite/mafenide/alginate films were applied as a bactericidal agent with effective wound-healing applications, and morphologically modified LDHs with lysozyme showed excellent antibacterial and wound-healing capabilities [129]. Due to the striking capabilities of the above-mentioned 2D NMs with outstanding bactericidal efficacy, they have gained more researchers' attention. A collective summary of antibacterial 2D NMs and their intended use is given in Table 1.

3.2. Surveying antibacterial mechanisms of functionalized 2D nanomaterials

2D NMs have been designed and functionalized in such a way that they support larger area disinfection and trigger-induced bacterial mechanisms. Widely studied antibacterial mechanisms for 2D NMs generally discussed two bactericidal strategies: physical destruction followed by oxidation of major functional systems (enzymes) that eventually cause cellular death. The major bactericidal modes of action include physical distress on bacterial cells *via* physical contact, photo-induced cellular damages *via* ROS generation, photothermal disinfection, Fenton reaction-assisted inactivation, and metal-ion release leading to cellular toxicity. Among these, the first three antibacterial mechanisms are reported as active antibacterial behaviors of 2D NMs, while the Fenton reaction and metal-ion releasing are the dominating mechanisms for 1D metal-based NMs [153].

Table 1
List of antibacterial 2D NMs and their intended use.

2D NMs	Synthesis	Strategy	Size/Max. Conc.	Bacteria	Intended use	Ref
GO-Ag-Fe_3O_4	Hummers' method	Synergistic: mechanical, metal toxicity	Fe_3O_4 (7–15 nm) Ag (30–50 nm) 6.25 μg/mL	*E. coli*, *S. aureus*	Antibacterial	[130]
Titanium modified with Minocycline-loaded GO	Chemical modification	Synergistic: mechanical, drug release	10 mm × 1 mm not detected	*S. aureus*, *S. mutans*, *E. coli*	Clinical application	[131]
rGO-WS_2	Hummers' method, hydrothermal reaction	Synergistic: mechanical, metal toxicity	1–3 μm × 1–5 nm 250 μg/mL	*E. coli*, *B. subtilis*, *S. typhimurium*, *S. epidermidis*	Pharmaceutical and industrial application	[132]
GDY/GDYO	Surface oxidation	Synergistic: mechanical, photothermal	GDY (410 nm × 4–9 nm) GDYO (370 nm × 4–11 nm) GDYO (3 mg/mL)	*E. coli*, *S. aureus*	Antibacterial	[133]
Ultrathin g-C_3N_4	Thermal etching, ultrasonic exfoliation	Photocatalysis	0.5 nm thick 0.1 g/L	*E. coli*	Water disinfection	[134]
AgBr-g-C_3N_4	Thermal polymerization	Photocatalysis	10–200 nm not mentioned	*E. coli*, *S. aureus*	Clinical application	[135]
Z-scheme g-C_3N_4/m-Bi_2O_4	Hydrothermal method	Photocatalysis	Bi_2O_4 (2–5 μm) 20 mg/50 mL	*E. coli* K-12	Water disinfection	[136]
Ag-Pd NS	Deposition techniques	Synergistic: photothermal, metal ion release	N/A	*E. coli*, *S. aureus*	Clinical application	[137]
Fe_3O_4-TiO_2 NS	Lamellar reverse micelles, solvothermal method	Photocatalysis	TiO_2 (0.32 nm) Fe_3O_4 (0.29 nm) 100 μg/mL	*E. coli*, *S. aureus*	Wastewater treatment	[138]
Ag/CS-MnO_2 NS	Hydrothermal method	Synergistic: photothermal, metal ion release	6 mm × 2.5 mm 200 μg/mL	*E. coli*, *S. aureus*	Clinical application	[139]
AuNR-Bi_2WO_6 NS	Hydrothermal method	Synergistic: photothermal, metal toxicity	540 nm thick AuNRs 25 nm Bi_2WO_6 50 nm N/A	*E. coli*, *S. aureus*	Clinical application	[140]
g-C_3N_4-MoS_2/Bi_2O_3	Hydrothermal-calcination method	Photocatalysis	29.5 nm 200 μg/mL	*E. coli*, *S. aureus*	Wastewater treatment	[141]
NiS-MoO_3/GO	Hydrothermal method	Photocatalysis	45.31 nm 200 μg/mL	*E. coli*, *S. pyogenes*	Industrial use	[142]
AgNC- MoO_{3-x} NS	Hydrothermal method	Synergistic: photothermal, photocatalytic, metal ion release	300 nm × 20 nm 1.125 mg/mL	*E. coli*, *S. aureus*	Wastewater treatment	[143]
MoS_2 NS coated on Ti substrate	Hydrothermal method	Synergistic: Catalytic, metal ion release	330 nm thick N/A	*E. coli*, *S. aureus*	Biomedical devices	[144]
Bi-doped MoS_2 NS	Hydrothermal method	Synergistic: catalytic, metal toxicity	55–72 nm 500–1000 μg/50 μl	*E. coli*, MRSA	Biomedical application	[145]
Zr-doped MoS_2 NS	Hydrothermal method	Metal toxicity	100 nm 0.5–1 mg/50 μl	*E. coli*, *S. aureus*	Industrial use	[146]
MoO_3-SiO_2-Ag_2O on Ti substrate	Double cathode glow discharge	Synergistic: photocatalytic, metal ion release	2.6 μm × 300 nm N/A	*E. coli*, *S. aureus*, *S. typhimurium*, *C. albicans*	Clinical application	[147]
ZnO/ZnSe/$MoSe_2$ NS	Hydrothermal method	Photocatalysis	20–50 nm thick N/A	*E. coli*	Industrial use	[148]
MoS_2-BNN6	Chemical modification	Synergistic: photothermal, NO release	133 nm 200 μg/mL	*E. coli*, *S. aureus*, *E. faecalis*	Tissue reconstruction	[103]
$Ti_3C_2T_x$ MXene	Ball milling, chemical modification	Catalysis	N/A 200 μg/mL	*E. coli*, *B. subtilis*	Water desalination	[149]
AuNR-LDH NS	Chemical synthesis	Synergistic: mechanical, photothermal	60 nm 100–300 μg/mL	*S. aureus*, *E. coli*	Clinical application	[150]
BP NS-PLEL (hydrogel)	Liquid exfoliation	Synergistic: mechanical, photothermal	288.3 nm × 23.4 nm 50 ppm	*S. aureus*	Cancer treatment	[151]
α-In_2Se_3 NS	Liquid exfoliation	Photothermal	300 nm 150 ppm	*E. coli*, *S. aureus*	Biomedical application	[128]
Sb_2Se_3 NS	Liquid exfoliation	Synergistic: mechanical, photothermal	50–150 nm 150 μM	*E. coli*, *S. aureus*	Biomedical application	[152]

Footnotes: m-, monoclinic; CS, hybridized chitosan; NR, nanorod; NC, nanocube; NS, nanosheet; GDY, graphdiyne; GDYO, graphdiyne oxide; BNN6, N,N′-di-sec-butyl-N,N′-dinitroso-1,4-phenylenediamine; PLEL, poly(d,L-lactide)-poly(ethylene glycol)-poly(d,L-lactide); α-In_2Se_3, indium selenide; Sb_2Se_3, antimony selenide; N/A, not available; MRSA, Methicillin-resistant *Staphylococcus aureus*. Size is explained as length × thickness followed by the maximum concentration of each material.

3.2.1. Enhanced physical interaction

Many studies have demonstrated that the bacterial cell wall and plasma membrane are the indispensable components responsible for maintaining cellular morphology, regulating osmotic pressure, and protecting cells. It has been proven that Gram-negative bacteria and Gram-positive bacteria have different cell wall compositions and structures. Gram-negative bacteria comprise distinct pairs of lipoprotein membranes separated by a thin layer of peptidoglycan in periplasmic space. On the other hand, Gram-positive bacteria possess a single lipid-bilayer of cellular membrane with multilayered thick peptidoglycan mesh outside the membrane [154]. It has been reported that the sharp edges of nanosheets, also known as nanoknives, probably acted as an

efficient bacterial killing tool by compromising their membrane integrity upon physical interaction. This physical damage could lead to the leakage of various intracellular components, such as nucleic acid, proteins, phospholipids, etc. [155] This antibacterial mechanism was primarily anticipated for graphene-based NMs. This type of contact between 2D NMs and bacterial cell walls or membranes might result in compromised membrane integrity, ROS-independent and ROS-dependent oxidative stress [156]. Three basic steps to determine bacterial inactivation are NM's binding with bacteria, membrane disruption, and inactivation of important cellular components [157]. Membrane stress-dominated antibacterial behavior of the nanohybrid system was reported by showing a synergistic antibacterial activity that caused ultrastructural damages in *E. coli* and *S. aureus* due to surface-edged Ag-NPs, with the bacterial trapping effect of GO nanosheets [158]. Similarly, the sharp edges and robust oxidative nature of ce-MoS_2 nanosheets with larger surface area offered efficient electron transfer pathways for bacterial interaction, which eventually cause membrane disruption and leakage of cellular constituents upon physical contact and ensure comparable antibacterial activity upon light irradiation by oxidizing glutathione in bacterial cells [159]. Lately, a new

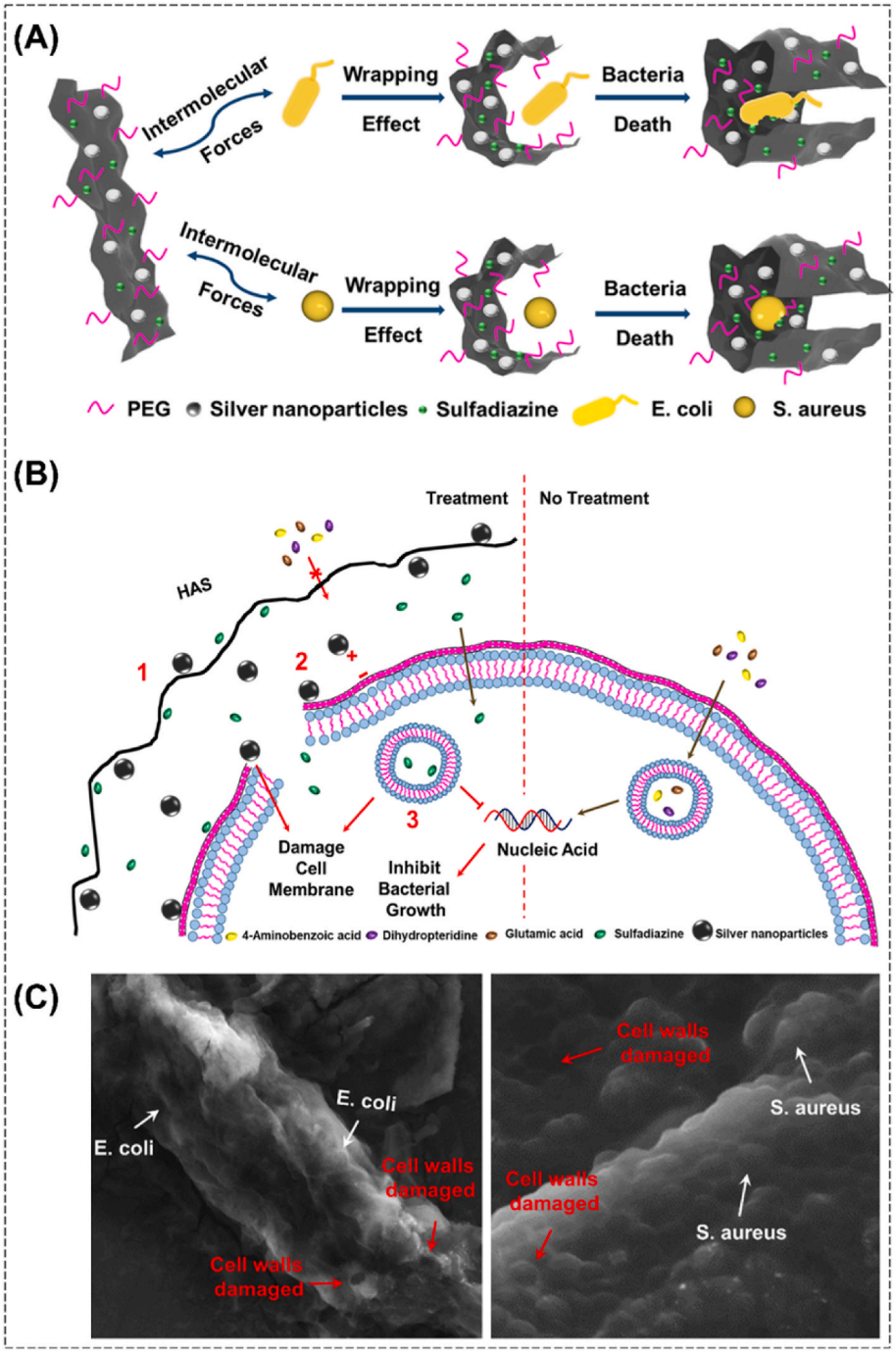

Fig. 10. (**A**) Schematic illustration of the interaction between HAS and microorganisms, (**B**) Illustrating their synergistic antibacterial mechanism, which is divided into three parts: (1) The capping effect of graphene oxide significantly increases the amount of Ag NPs and SD around bacteria and competitively blocks the nutrient transport, whereas (2) the physical pricking by Ag NPs causes the additional antibacterial effects of SD that (3) inhibits the synthesis of bacterial nucleic acid and cause deterioration of cell wall, (**C**) SEM images of *E. coli* cells "A" and *S. aureus* cells "B" treated with HAS (50 μg/mL) for 1 h. Reproduced with permission [79].

family of 2D NMs $Ti_3C_2T_x$ MXenes has been reported that exhibited an excellent antibacterial property by stress-dominating membrane disruption and leakage of intracellular constituents causing cell death by nanoknives effect against *E. coli* and B. *subtilis*. In conclusion, stress-induced bacterial killing *via* physical contact is a reasonable antibacterial mechanism [149,160]. However, novel nanosystem approaches have been introduced in the presence of external stimuli (light) and surface-edged nanoparticles, which exhibited comparatively significant bactericidal effects. Such a hybrid antibacterial system (HAS) exhibited improved antibacterial performance by using triple synergy *via* bacterial capping (GO) and membrane puncturing (AgNPs), with inhibitory effects of sulfadiazine mentioned as SD in Fig. 10 [79].

3.2.2. *Multifunctional synergistic approach*

Various antibiotic-free antibacterial mechanisms have been introduced in the last two decades, including two major bactericidal strategies, "active antibacterial killing" and "light-induced antibacterial strategy". The former strategy is explained in *Section 3.2.1* as it involves direct contact between bacterial cells and nanomaterials and is responsible for physical disruption but demands a longer time for bacterial decomposition. This is why many researchers and biomedical scientists switched focus to studying the physical stimuli-based antibacterial approaches, including light-induced bactericidal strategies, such as ROS-triggering photothermal therapy (PTT) and photodynamic therapy (PDT). Generally, the photo-induced antibacterial strategies employed the conversion of excited photoactive fluorophores in photosensitizers, photothermal agents, or in any other semiconductor NMs into heat or ROS for photothermal, photochemo, or photodynamic therapies [149,161]. These photo-induced antibacterial therapies have recently been considered promising antibacterial approaches due to their peculiar merits, like non-invasiveness, targeted selective treatment, and minimal side effects. We will shortly discuss two types of photo-induced antibacterial strategies (i.e., photothermal and photocatalytic antibacterials) as these are some of the most applicable strategies in the mainstream approach to combat systemic antibiotic resistance.

The *photothermal antibacterial* process refers to the efficient heat generation by NMs under light irradiation at a low power density for bacterial inactivation. Near-infrared (NIR) light is preferred for antibacterial photothermal disinfection due to its deep penetrating capacity across biological tissues with minimal damage to the uninfected areas [162]. This type of antibacterial mechanism was employed by several NMs owing to their robust photothermal conversion efficiencies, including metallic NPs (Au, Pt, etc.), metal chalcogenides (Bi_2S_3, MoS_2, CuS, Sb_2Se_3, etc.), LDH-based compounds, BP nanosheets, and carbon-based NMs [163,164]. Among 2D carbon-based NMs, reduced

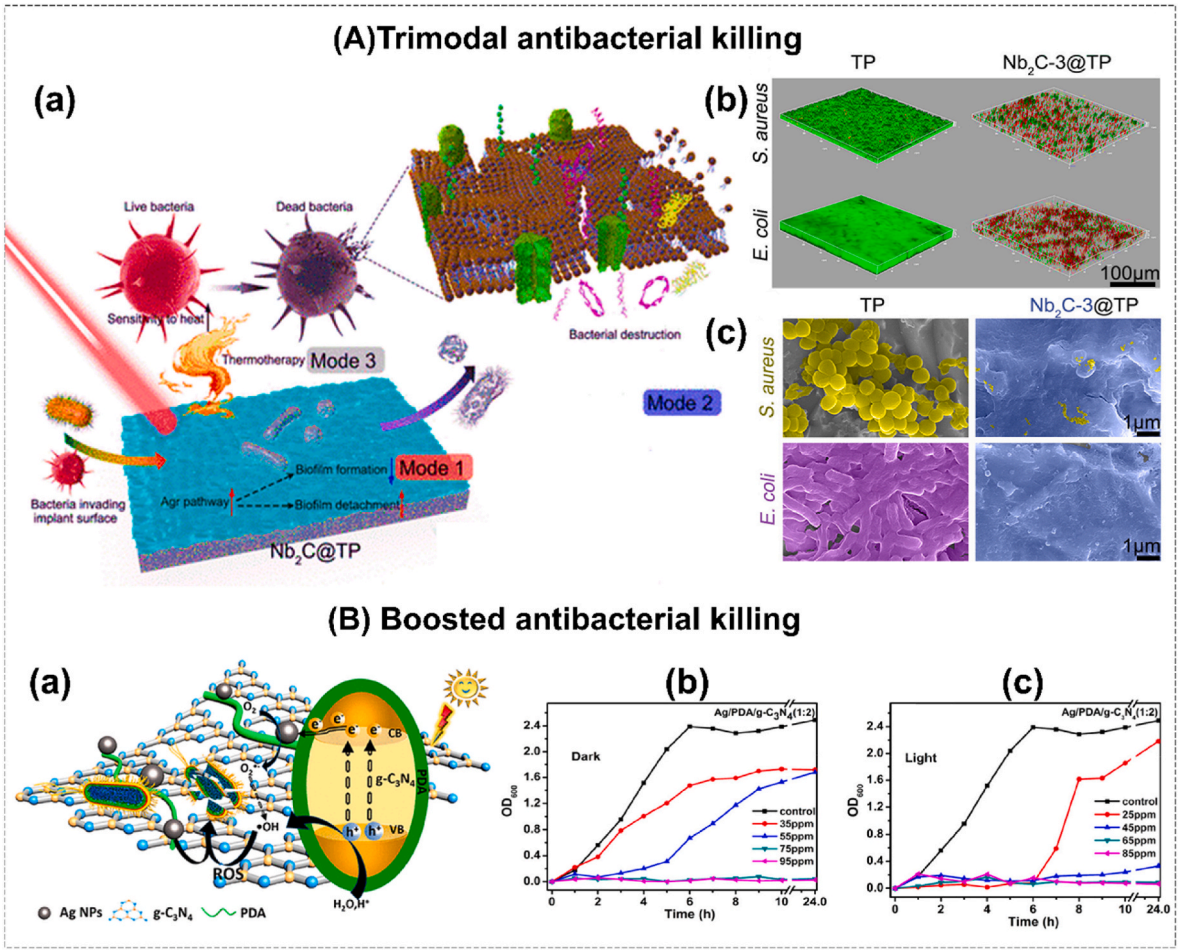

Fig. 11. **(A)** Multimodal antibacterial activity of MXene titanium plate (NTP)-based thermotherapy: **(a)** Schematic illustration of trimodal bacterial killing strategy involving biofilm resistance, intrinsic bactericidal effect, and thermoablation of bacteria, **(b–c)** Confocal 3D images of biofilm (green color indicates live bacteria and red color indicates dead bacteria), SEM images of biofilm formed by *S. aureus* and *E. coli* in the absence and presence of Nb_2C@TP nanomaterials. Color representation: *S. aureus* (yellow spheres), *E. coli* (violet rods), TP (gray color), and Nb_2C NSs (royal blue color). Reproduced with permission [110]. Copyright © 2021, American Chemical Society, (**B**) **(a)** Illustration of an advanced antibacterial photocatalytic mechanism of PDA modified g-C_3N_4 nanosheets loaded with AgNPs biophotocatalyst, **(b–c)** Enhanced antibacterial killing curve for *E. coli* under dark and visible light irradiation using serial concentrations of g-C_3N_4, PDA/g-C_3N_4, and Ag/PDA/g-C_3N_4. Reproduced with permission [87]. Copyright © 2018, American Chemical Society.

graphene oxide (rGO) nanosheets are the most utilized photothermal disinfecting nano-agents. They showed excellent light-to-heat conversion efficiency upon IR light irradiation and exhibited significant bacterial killing [164]. Additionally, Cu-based chalcogenides favored cheap photothermal antibacterial strategies by fabricating CuS in the presence of bovine serum albumin, which exhibited significant biocompatible and excellent bactericidal capacity when irradiated at 980 nm under NIR range [165]. In this direction, MXenes are the emerging 2D NMs exhibiting appealing physiochemical properties (i.e., catalytic, photoelectric, magnetic, etc.) and captivating ultrathin structures. This group of NMs exhibits a wide range of light absorption capacity (from UV to NIR) and excellent biocompatibility with superior photothermal effect, which make them a most suitable candidate for light-responsive antibacterial therapies [166,167].

The illustration of trimodal bacterial killing (mode 1: biofilm resistant, mode 2: intrinsic bactericidal effect, and mode 3: thermoablation of bacteria) is given in Fig. 11 (A), showing significant bacterial eradication with maximum bactericidal impact [110]. Moreover, the NIR-triggered heterostructure catalyst, comprised of 2D MXene and 1D CoNWs (cobalt nanowires), can easily induce synergistic antibacterial effect when applied as a drug-free therapy for bacterial eradication under 808 nm NIR irradiation, exhibited 80.1 % and 92.74 % respective antibacterial efficiencies toward *E. coli* and *S. aureus* [167]. Similarly, a few other strategic nanohybrid systems were also represented to remove bacteria using GO nanosheets as major nanoplatforms [104,110,168].

The *photocatalytic antibacterial* process has recently emerged as an effective solution for disinfecting various pathogenic organisms. The 2D graphitic carbon nitride (g-C_3N_4) material has emerged in the photocatalytic disinfection field as it can harvest a substantial amount of visible light to achieve higher photocatalytic activity [71]. Recently, g-C_3N_4 nanosheets revealed exceptional photocatalytic antibacterial properties against *E. coli* upon visible light irradiation, which did not show the regrowth of bacterial colonies [88]. Moreover, metal-based 2D NMs (MoS_2, TiO_2, Bi_2WO_6, ZnO) and metal-free 2D NMs demonstrated excellent photocatalytic antibacterial properties [73]. Different combinations of co-catalysts have been widely inspected as an effective modified antibacterial strategy, which includes g-C_3N_4 NS/RGO, V_2O_5/$BiVO_4$, Ag-ZnO/g-C_3N_4, TiO_2/g-C_3N_4, graphene/g-C_3N_4, TiO_2--Bi_2WO_6, and Bi_2MoO_6/g-C_3N_4 [85,169]. We have shown enhanced antibacterial photocatalytic activity of bio-photocatalyst i.e., PDA-modified Ag-loaded g-C_3N_4 nanosheets, demonstrating photogenerated holes generated under brilliance move toward the surface in the presence of self-generating electric fields representing a higher charge separation efficiency, which reinforces the trapping effect of Ag metal on photogenerated electrons, the enhanced antibacterial photocatalytic mechanism, is shown in Fig. 11B with supporting graphs [87]. In addition, these photogenerated holes and electrons react with O_2 and H_2O to produce ROS (including $\cdot O_2^-$, H_2O_2, and ·OH), which diffuse into the bacterial surroundings and eventually cause cellular death [86]. Even though photocatalytic disinfection is one of the most efficient disinfection mechanisms, it still deals with important issues such as catalyst immobilization, photocatalytic reactor design, recycling procedures, and optimization of disinfection parameters of new materials require to be addressed for practicable applications shortly [167].

Besides photothermal and photocatalytic disinfection methods, the Fenton process can be exploited to achieve a significant antibacterial, antifungal, and antiviral agent. However, it lacks standardized procedures for reporting heterogeneous catalytic activities and is concerned with catalyst stability and longevity [170]. However, various novel 2D NMs possess photothermal properties that have not yet been explored. These burgeoning photothermal NMs with strong NIR light conversion capacity disclosed that the successfully converted heat could not only kill drug-resistant bacteria but may also inhibit biofilm formation. Therefore, the 2D NMs-based photothermal disinfection method is deemed safe and effective in combating bacterial infections.

3.2.3. Metal-ion functionalization

Metal-based NMs can release metal ions upon bacterial interaction, crossing the bacterial cell membrane and disrupting cellular components. These metal ions for disinfection have been accepted as one of the antibacterial modes of action of metal-based NMs, which is normally a part of physical and synergistic antibacterial mechanisms [171]. For example, the noble metal cation (Ag^+) can directly inhibit the functions of major cellular enzymes by binding to their thiol groups. In addition, Ag^+ acts as a nucleic acid binder and can denature nucleic acid (DNA) while inhibiting its major replication process, which eventually causes bacterial cell death. In the case of bactericidal 2D NMs, the modes of action are often combined with other methods, such as chemical functionalization and physical disinfection [172]. Recently, a group of researchers proposed a novel nano-conversion strategy for improved antibacterial activity by converting natural organosulfur compounds into nano-iron sulfides (FeS), where the improved antibacterial effect benefits from cysteine-nFeS (Cys-nFeS) with enzyme-like activity, which could efficiently increase the bactericidal polysulfanes release. This study revealed that the intricate Cys-nFeS NMs are a significant antibacterial agent against *E. coli*, *S. aureus*, and *P. aeruginosa*. They could also efficiently inhibit biofilm formation while accelerating infected wound healing [173]. Furthermore, Cao et al. designed an efficient and benign bactericidal depot with cysteine-modified MoS_2 loaded with Ag^+ and coated with polyelectrolyte, i.e., poly(dimethyldiallylammonium chloride) (PDDA-Ag^+-Cys-MoS_2). Their system achieved remarkable bactericidal activity against *E. coli* and *S. aureus* due to the enhanced accessibility of released Ag^+ across bacterial cell membranes compared to the equivalent amount of silver nitrate [174]. Moreover, in synergy with NIR photothermal therapy, Pd@Ag nanosheets damage bacterial cells and trigger AgNPs by absorbing light to release Ag^+, which improves their disinfection performance. These released metal ions usually interfere with essential cellular processes by compromising cell membrane integrity, enzyme malfunctioning, and inhibiting cellular components responsible for respiration, replication, and energy production in adenosine triphosphate (ATP) [97,173]. However, these released metal ions should be used in the lowest concentrations to a suitable range to avoid human cytotoxicity. For good measure, the effective removal of metal ions and metal-based NMs is also required for their practical implementation.

3.2.4. Additional antibacterial hypotheses

The biological interaction between NMs/NPs and bacteria is convoluted, so other mechanisms besides the antibacterial mechanisms have been proposed. We must understand the different antibacterial approaches and their causing agents (metal ions, ROS species) among bacterial cells to address these points. Principally, metal-based NMs could catalyze site-specific damages to cellular proteins by inducing protein dysfunction and enzymatic impairment, such as loss of activity. This type of damage might be responsible for metal toxicity among cellular organisms [175]. For example, toxic Cr(vi) doses induce ROS-dependent protein dysfunction by increasing the protein carbonyl levels in *S. cerevisiae* within a few minutes. The increased levels of carbonyl groups are usually associated with oxidative stress in proteins [176]. In addition to the metal-based NMs/NPs, 2D NMs consist of 2D graphene oxide (GO) and molybdenum disulfide (MoS_2) induced ROS-independent oxidative stress (cell membrane damages) and ROS-dependent oxidative stress toward bacterial cells (*via* glutathione dysfunction). While explaining intricate biological interactions between 2D NMs and bacteria, Tu et al. reported that graphene and GO nanosheets cross the bacterial cell membrane, interact with the lipids, and instigate lipid extraction. Such type of extraction directs membrane destruction and reduces bacterial viability. These 2D graphene-based NMs have been observed to interfere with intracellular signal transduction and cellular metabolism by affecting protein-protein and NMs-proteins interactions [177]. Moreover, another interesting antibacterial mechanism has been proposed, known as the “suicide effect”.

Bacterial cells remove the oxygen-containing functional groups from graphene-based NMs (e.g., GO) *via* a glycolysis-like pathway and get demolished [178]. In addition to the protein dysfunction antibacterial mechanism, we will shortly discuss the transcriptional arrest, which greatly enhances DNA damage.

Graphene-based NMs contribute to induced protein dysfunction and transcriptional arrest, which are not the typical primary antibacterial mechanism of action. Santhosh et al. demonstrated significant protein degradation in the presence of graphene-Fe_3O_4 composite nanostructures (G-Fe_3O_4) compared to Fe_3O_4 alone, which can be seen through SDS-PAGE. The bacterial cells treated with G-Fe_3O_4 showed only a single band, whereas bacterial with graphene demonstrated multiple bands, highlighting the protein aggregation capabilities (disulfide formation) of G-Fe_3O_4 [179]. Furthermore, Akhavan et al. determined that the graphene-tungsten oxide (G-WO_3) composite nanostructures displayed enhanced photocatalytic protein degradation compared to WO_3 NPs alone using the same method [180]. Another study demonstrated that the interactions between DNA and

Table 2
Summary of antibacterial strategies based on the stimuli type and NMs.

Stimuli type		NM's type	Bacteria	Animal model/Cytotoxicity	Ref
Physical stimuli					
Mechanical:	Mechanical	Cicada nanopillars	*P. aeruginosa*	N/A	[183]
	Stretching	Titanium nanopillars	*K. pneumoniae*	N/A	[184]
		Nanowires and nanocones	*S. aureus, B. subtilis, P. maritimus*	N/A	[48]
	Cutting (nanoknife)	Graphene nanowalls and nanosheets	*E. coli, S. aureus*	N/A	[185]
		BN nanosheets	Model membrane	N/A	[186]
		PMMA pillared films	*E. coli*	N/A	[187]
	Capture (sterilization)	Polycrystalline NWs with nanoclaws on 3D CF	*Salmonella* spp.	N/A, Non-toxic	[188]
		PDMS chips *via* cell imprinting	*E. coli, B. subtilis*	N/A	[189]
		Lysozyme-loaded silica nanopollens	*E. coli*	*Ex vivo* (small intestine model), Non-toxic	[190]
Optical:	Photocatalytic therapy	TiO_2/GDY nanofibers under UV light	MRSA	Kunming mice, Non-toxic	[191]
		TiO_2/Au NPs under NIR irradiation	*E. coli,* MRSA	N/A, Non-toxic	[192]
	Photodynamic therapy	pMOF- MnO_2 nanoplatform	*S. aureus, E. coli*	Mice (subcutaneous abscess), Toxic	[193]
		SiO_2/PAH-Ce6 under NIR irradiation	*S. aureus, E. coli,* MRSA	N/A	[194]
	Photothermal therapy	SiO_2-Cy-Van under NIR fluorescence	MRSA	Female Balb/c mice, Non-toxic	[195]
		Au@TA NP/PEG under NIR irradiation	*S. aureus, E. coli*	Female SD rats, Low toxicity	[196]
		Carbon-Fe_3O_4 under NIR irradiation	MRSA, *S. aureus*	Wistar male rats, Non-toxic	[197]
Magnetic:	Combined therapy	Fe_3O_4-ZnO NC under AC magnetic field	*E. coli, S. aureus*	N/A	[198]
		Au/$MnFe_2O_4$ under magnetic heating	*S. aureus, B. subtilis, E. faecalis, S. pyogenes*	N/A	[199]
Acoustic:	Sonodynamic therapy	RBC-HNTM-Pt@Au	MRSA	Male Sprague-Dawley rats, Non-toxic	[200]
		Au@ $BaTiO_3$ NC	*E. coli, S. aureus*	Female mice, Non-toxic	[201]
Electrical:		CuO NW-Ag NP *via* electroporation	*E. coli, S. aureus*	N/A	[202]
		CFFs modified Au-Te nanowires *via* TENG	*E. coli, S. aureus*	N/A	[203]
Chemical stimuli					
	Metal ion release	AgNPs (Ag^+)	*E. coli, S. aureus*	N/A, Toxic	[204]
		AgNPs/AMP sustained polymersomes	*S. aureus,* MRSA	N/A, Non-toxic	[205]
		NPs of Ag, CuO, Cu_2O, TiO_2, ZnO, Fe_2O_3, Al_2O_3	*E. coli, S. aureus*	N/A	[206]
	Cationic interaction	SNAPPs	CMDR, MDR	Non-Toxic	[207]
		CB-ring/CB-OH polymer	*E. coli* K12	N/A	[208]
		PDA/poly(MPC/META)	*S. aureus, E. coli*	N/A	[209]
	Site-specific binding	MSNs⊂Lys (surface hydrolysis)	*E. coli*	BALB/c mice, Non-toxic	[210]
		$AgPd_{0.38}$/$AgPd_{0.38}$@lipid (surface-bound ROS)	*P. aeruginosa* PAO1	N/A, Non-toxic	[211]
	ROS	Cu_2WS_4 nanocrystals	MRSA, *S. aureus*	N/A, Low toxicity	[212]
		$AgPd_{0.38}$ nanocage	*P. aeruginosa* PAO1, *B. subtilis, E. coli*	ICR female mice, Non-toxic	[213]
		SAzymes ZIF-8	*P. aeruginosa*	Mice, Non-toxic	[214]
Combined platforms					
	pH-sensitive	AuNPs triggered under NIR irradiation and acidic biofilm	MRSA biofilm	N/A, Non-toxic	[215]
		CHX-SiNPs (triggered drug release at pH of 8.0 and 8.5)	*S. aureus, E. coli*	*Ex vivo* human skin, Non-toxic	[216]
	Temperature-sensitive	Thermoresponsive PINAM-modified-MOFs	N/A	N/A	[217]
		POEGMA188	*E. coli, S. aureus*	Non-toxic	[218]
	Multi-functional	Ti-S-TiO_2-x with sonodynamic, photodynamic, and photothermal functions	*S. aureus*	Wistar male rats,	[219]
		Nanobot-specific Fe_3O_4/SiO_2 NPs with RF-EMS functions	MRSA	Non-toxic	[220]
		Fe-Artificial Macrophage (capture killing/ROS)	MRSA	Mice, Low toxicity	[221]
		PDA/Ag_3PO_4/GO (photocatalytic/Ag^+ release)	*S. aureus, E. coli*	New Zealand white male rabbit, Non-toxic Male Sprague-Dawley rats, Non-toxic	[222]

Footnotes: NP, Nanoparticle; NC, nanocomposite; MRSA, Methicillin-resistant *Staphylococcus aureu*; PMMA, poly(methyl methacrylate); NWs, nanowires; CF, carbon foam; PDMS, polydimethylsiloxane; SNAPPs, structurally nanoengineered antimicrobial peptide polymers; CMDR, colistin-resistant MDR; cationic CB-ring, N,N-dimethyl-2-morpholinone; zwitterionic CB-OH, carboxy betaine; PDA/poly(MPC/META), polydopamine/poly(MPC-st-MAABO)/poly(META-st-MAABO); MSNs⊂Lys, lysozyme-coated mesoporous silica nanoparticles; SAzymes, single-atom nanozymes; CHX-SiNPs, chlorhexidine-silica nanopartilces; PINAM, poly(N-isopropylacrylamide); POEGMA188, poly(di(ethylene glycol)methyl ether methacrylate); PAH, poly(allylamine hydrochloride); pMOF, Porphyrin-MOF; Cy-Van, cypate-vancomycin complexes; PEG, polyethylene glycol; TA, tannic acid; RBC-HNTM-Pt@Au, red cell membrane coated Au/Pt single-atom-doped porphyrin metal-organic framework; CuO NW-Ag NP, CuO nanowire with silver nanoparticle, TENG; triboelectric nanogenerators; CFFs, Carbon fiber fabrics; RF-EMS, radiofrequency electromagnetic stimulation; SD, Sprague-Dawley;N/A, not available.

graphene-based (GO) NMs reduce supercoiling by encouraging the formation of nicks and linearized DNA [181]. GO nanosheets provide a platform for Cu^{2+} chelation due to the presence of oxygen-containing functional moieties on GO, which allows proficient delivery of Cu^{2+} to DNA molecules. These GO nanosheets intercalate between the DNA base pairs (π–π stacking interactions), enhancing the chances of Cu^{2+} delivery to DNA molecules by GO nanosheets. Such transcriptional arrest causes DNA cleavage based on the Cu^{2+} interaction with heterocyclic nitrogen groups (soft bases), which catalyze hydrolytic cleavage of the phosphodiester backbone of DNA molecules, leading to the observed cleavage [182]. These studies provide evidence of significant additional antibacterial mechanisms observed using graphene-based NMs [179]. A summary of antibacterial strategies based on the stimuli type, NMs, and cytotoxicity is given in Table 2.

3.3. Biomedical significance of 2D NMs

3.3.1. Dysbiosis and nanotoxicity

NMs (including 2D NMs) have been utilized in food, pesticides, electronics, and medicine, among many others, due to their unique physicochemical and biological properties. However, NMs can translocate into systemic circulation by penetrating the human skin, lungs, and gastrointestinal tract (GIT) and eventually distribute to various body parts (tissues, organs) [223]. In addition, they can modify gut microbiota or microbiome (GM), which plays a key role in maintaining human health, including immunity, metabolism, neurobehavioral developments, and several others [224]. The disturbance in natural GM configuration is known as GM dysbiosis, and it is associated with human diseases and medical conditions, such as asthma, central nervous system disorders, diabetes, and inflammatory bowel disease (IBD) [225]. Moreover, medical formulations containing several NMs (organic polymers, carbon nanotubes, micelles, liposomes, and inorganic NMs) may cause significant damage to the human gut, particularly due to long-term exposure to NMs. NMs' exposure to the human gut is not only expected *via* the oral route; the negative impact on GM may also be the consequence of absorbed NMs from mucociliary clearance, inhaled materials, and intravenous injections [226]. In addition to the latter example, a considerable amount of AgNPs was detected from laboratory rats' fecal excretions following intravenous administration [227]. The available reports have interpreted the possible toxicological effects of NMs on GM and showed their potential clinical consequences. Although the available data have not only suggested adverse effects of consumed NMs, they have also shown the advantages of nanoscale materials (iron NPs) over their traditional alternate treatment (iron-based supplement) as they do not interfere with GM [228]. Various investigations have been inferred on NMs' impact on GM; however, in certain cases, these analyses yield contradictory results for the same type of NM, which usually follow various methods and approaches during the investigation. Although several reports have been done on the subject matter, a systematic evaluation of NMs' impact on GM in various species is required. Utembe et al. retrieved data from 46 *in vivo* and 22 *in vitro* dysbiosis analyses from the available resources and assessed NMs' effect on GM configuration based on NMs' characterization, used number of doses, and consistency of desired results. GM dysbiosis has been studied most in cases of Ag, TiO_2, Zn, and Cu-based NMs. These NMs showed moderate evidence for causing dysbiosis, while low evidence was inferred for nanocellulose, carbon nanotubes, Se, SiO_2, CeO_2, MoO_3, and graphene-based NMs. For further elucidations on the reported impacts of NM, a few key parameters needed to be considered additionally, including NM's size, shape, type, exposure time, and sex of test organisms.

For further understanding of nanotoxicity and biotransformation of NMs, it is important to track their location under physiological conditions [229,230]. The translocation of ingested NMs is usually carried through GIT, during which they encounter various surface-active molecules (proteins, phospholipids, mucin, and bile salts) and specific biochemical surroundings while moving through three main GIT sites, such as mouth with pH 6.7–7.0, stomach (pH 1.5 and 2.5), and small intestine (pH 6.0–7.0) [231,232]. These NMs can adsorb proteins, lipoproteins, lipids, and other molecules on their surfaces by forming a crown-like structure known as the bio-corona [230]. At the same time, they sequentially encounter different environments across GIT and undergo transformations influencing their physiochemical properties (size, surface charge, available surface area, shape, agglomeration state, and dissolution kinetics), which regulate nano-bio interactions and nanotoxicity [233]. One of the most common causes of nanotoxicity for metal-based NMs is the release of metal ions by dissolution upon exposure to distinctive chemical environments [234]. Depending on their physicochemical properties, ingested NMs were usually taken up *via* cellular endocytosis and translocated across the small intestine (SI) via transcellular or paracellular paths. Further investigations confirmed that the NMs with diameters <100 nm can enter cells, and smaller NMs with diameters <40 nm can enter the nucleus [235]. Using a stimulated three-phase digestion model (oral, gastric, and small intestinal) to assess the biotransformation of surface-active materials, including graphene, GO, partially reduced (prGO), reduced (rGO), h-BN, MoS_2, and WS_2 2D NMs for the evaluation of ingested NMs on the integrity of epithelial layer, viability, cytotoxicity, oxidative stress, and apoptosis. Nevertheless, the occasional ingestion of small doses of NMs might not be significantly cytotoxic in physiologically relevant *in vitro* GIT models. However, their genotoxic potential remains unclear after short or long-term exposure to NMs, which requires to be investigated in future studies [231]. Conclusions cannot be drawn from the available data as NMs might cause various damages in the gut tissues and induce GM inflammation after overcoming the protection layers; a detailed illustration was drawn that can show the significant apparent impact of NMs on the gut and GM (Fig. 12).

To determine gut nanotoxicity and inflammation, the mice models were used to examine bio-accumulation of Mo after exposure to micro-MoS_2 and nano-MoS_2, which exhibited Mo accumulation in the main organs, exclusively in the large intestine (LI) and SI. However, nano-MoS_2 exhibited a higher intestinal inflammation than micro-MoS_2 with a higher bioavailability rate. Primarily, these NMs were engaged in carbohydrate and amino acid metabolism and significantly altered the configuration of microbial-host co-metabolites in SI and LI, respectively. That further suggested that nano-MoS_2 could change the intestinal metabolic profiles by influencing the microbial communities and causing direct intestinal toxicity. At the same time, micro-MoS_2 exposure only alters the metabolome profile (the potential relationship of the metabolic profiles based on microbial-host cometabolites [236]. From changes in intestinal microbiome and metabolic profiles, we may infer that integrating NMs in organisms is one of the main root causes of gut nanotoxicity and dysbiosis. We inferred the likely potential indirect relation of NMs with gut microbiota and gut nanotoxicity is due to the changes in the gut microbiome, gut metabolome, and metabolic profile of various biological molecules, including carbohydrates, amino acids, and lipids leading to cellular inflammation and dysbiosis, an illustration explaining the co-relation between them, is provided in Fig. 13.

Contrarywise, the therapeutic effect of biocompatible nano-enriched MoS_2 (NR-MoS_2) nanosheets was found efficacious in treating intestinal infection, with a significant reduction in *S. aureus* biofilm formation. A cutting-edge concept and mechanism of nanohole-boosted electron transport antibiofilm and anti-infection treatment was proposed that showed an ambiguous exfoliation of intestinal mucosa after treatment with NR-MoS_2, as compared with the *S. aureus* infected tissues but also cured ocular wounds of infected rats with the complete restoration of visual sensitivity and eye-sight. Furthermore, they also exposed the activation of specific gene regulators, which aid in antibacterial performance by ensuring biofilm detachment in the treated parts [104].

Moreover, adding to the state-of-the-art 2D carbon nanosheets has verified 100 % bactericidal proficiency even at low doses, demonstrating speedy recovery from wound infection via non-invasive synergetic

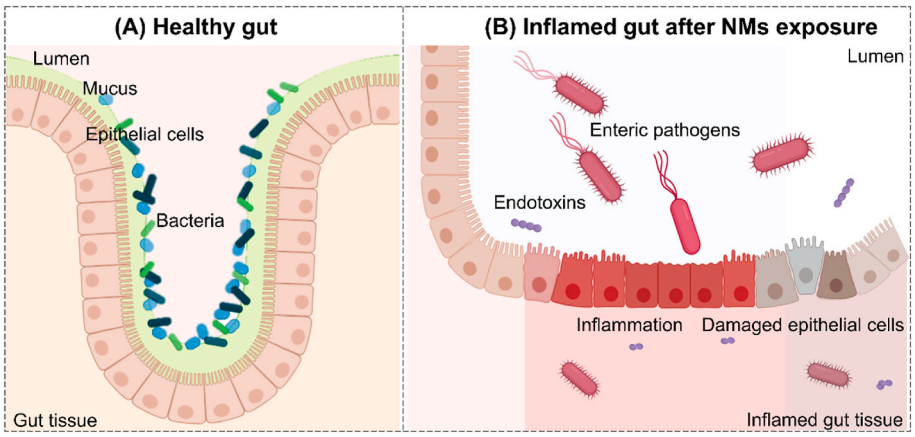

Fig. 12. Impact of NMs on the gut barrier and their likely pitfall in causing gut nanotoxicity and dysbiosis **(A)** Healthy gut, **(B)** Inflamed gut after NMs exposure. Created with BioRender.com.

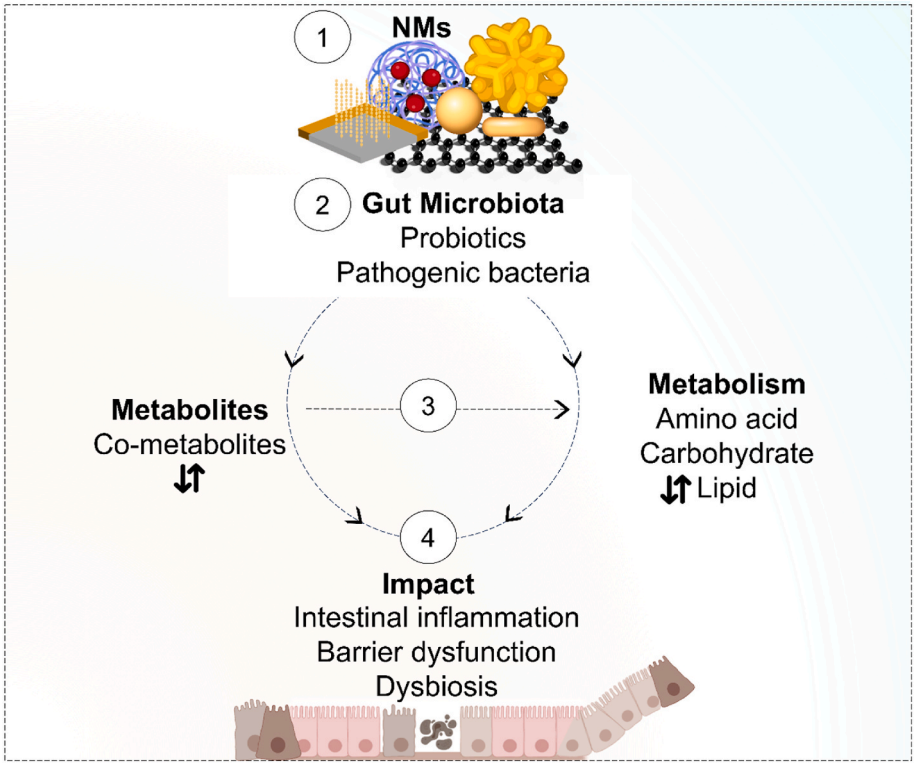

Fig. 13. The impact of NMs and their co-relation with gut-microbiota and gut-metabolome represented in 4 major steps such as **1)** NM exposure, **2)** interaction with gut microbiota, **3)** causing changes in metabolites and metabolism leading to **4)** intestinal inflammation, barrier dysfunction, and dysbiosis. "↑↓" showing changes in the form of up and down-regulation of associated genes and protein expression.

photothermal treatment exhibiting antibacterial potential against pathogenic bacteria. Nevertheless, contradictory results have been reported for NMs' evaluation and their effect on GM, intestinal integrity, and immunity. This may be associated with several inconsistencies, such as variation in *in vivo* model organisms, mode of exposure, dose and time-dependent exposure, and distinctive physicochemical properties of NMs. Moreover, the adapted methodology for GM analyses is another important point to consider before following any *in vivo* procedures. In this regard, a uniform model should be premeditated to investigate the critical impact of NMs on GM. The drawbacks of currently employed model organisms with different health consequences are the other key issues affecting the impact of NMs when analyzing human GM. This is mainly due to the important differences in GM of humans and other employed model organisms in terms of species, genus, and physiological functions of each GIT segment [237].

3.3.2. 2D NMs as drug delivery systems

By following the research focus and trend, we can understand the potential of 2D NMs as research hotspots in biomedical applications. Lately, 2D NMs-based nanomedicines (nanocarriers, drug delivery) have been widely used in targeting cancerous cells, biological protection, tissue engineering, bioimaging, cardiovascular and neurodegenerative diseases, and treating bacterial infections [238]. 2D NMs possess a thickness of a single to few atomic layers with lateral dimensions that create the maximum specific surface area and provide many contact points to increase the propensity of surface interactions of material with

drugs for drug-loading and controlled release kinetics. Moreover, drugs can be loaded *via* π–π stacking by stabilizing drug molecules and regulating stimuli-responsive release [239,240]. Current research has shown that 2D NMs improved the delivery of hydrophobic drugs by reducing cytotoxicity and increasing the bioavailability and drug efficacy. Moreover, their anisotropic charge distribution, high surface-to-volume ratio, and photodynamic and thermal properties make them potential delivery carriers while maintaining the therapeutic concentration of drugs at the target site. Additionally, the variation in energy band gaps and other physicochemical properties of 2D NMs are different, allowing designs of customizable drug delivery systems [239,241].

Graphene-based NMs demonstrated higher loading capacity, tuneability, biodegradability, and controlled release of small molecular drugs. These materials are widely investigated for their ability to release and sequester larger biomolecules. According to a recent study, the single-stranded G-quadruplex modified GO catalytic DNAzyme achieved efficient controlled therapeutic anticancer effects *in vivo* with the self-degradation capability. The chemotherapeutic drug doxorubicin was loaded onto the G-quadruplex DNA strands and then imprinted on the GO surface. The photothermal effect of GO causes the DNA to denature and consequently release the drug under NIR irradiation. Moreover, the high hydrogen peroxide concentration in the tumor environment degrades GO and rapidly clears the target site. This *in vivo* examination proved the anticancer property of GO and inhibited tumor growth, which is attributed to its inherent properties and surface modification [242]. A similar study used h-BN nanosheets to load and deliver doxorubicin *via* growing palladium NPs on its surface (Pd@OH-BNNS). A pH-responsive and NIR-dependent photothermal therapy was used at the target site to ensure sustainable drug release, inhibiting tumor growth and improving the drug loading and releasing capacity [243].

TMDs and MXenes NMs stand out among 2D NMs owing to their extraordinary properties. They can provide a new platform for developing drug delivery systems targeting bacterial infections and cancer. Such as multi-layered MoS_2 nanosheets and their application as nanocarriers for synergistic cancer therapy were achieved *via* surface functionalization with two different DNAs loaded with doxorubicin. Both DNAs combined with MoS_2 showed a significant increase in apoptotic cell population compared to free doxorubicin [244]. Also, TMDs possess intrinsic antibacterial properties that can be further investigated with similar agents for synergistic and enhanced biomedical effects. For example, nanocomposite films of MoS_2 and GO demonstrated improved *in vitro* antibacterial activity [102]. Besides, chemically modified MoS_2 nanosheets with indocyanine green can be used in tumor molecular imaging as a contrast agent, which can significantly improve the sensitivity of photoacoustic imaging, demonstrating an effective visualization of deep glioma [245] detailed scheme is given in Fig. 14 (A). In another study, MXenes (polyacrylamide hydrogel)-modified Ti_3C_2 nanosheets showed a significant increase in their mechanical properties and enhanced release of chloramphenicol. This could be achieved due to the incorporation of the MXene nanosheets with uniform pore distribution, which not only strengthens the mechanical attributes of hydrogel but also provides a larger interactive surface for drugs, making them a promising nanocarrier for drug delivery [246].

2D NMs such as BP and LDH are some of the less likely explored materials in this area, whereas these materials exhibited improved antimicrobial and anticancer therapies when combined with other agents. In a recent report, BP nanosheets loaded with titanium aminobenzenesulfanato complexes (Ti-SA_4@BPs) showed improved antibacterial activity against drug-resistant bacteria. This could be attributed to the planner *p* type-Ti coordination between Ti-SA_4 and BPs, which led to the high loading capacity of the drug (up to 43 %), positively charged surface of Ti-SA_4@BPs assisted in binding to the negatively charged bacterial cells while its sharp and pointed edges caused cell membrane damages in relative to the free BP and Ti-SA_4 [117]. Moreover, BP nanosheets can strongly bind to metal ions (due to phosphorous) and can be used as a neuroprotective drug delivery system to treat neurodegenerative diseases. BP nanosheets can cross the blood-brain barrier and

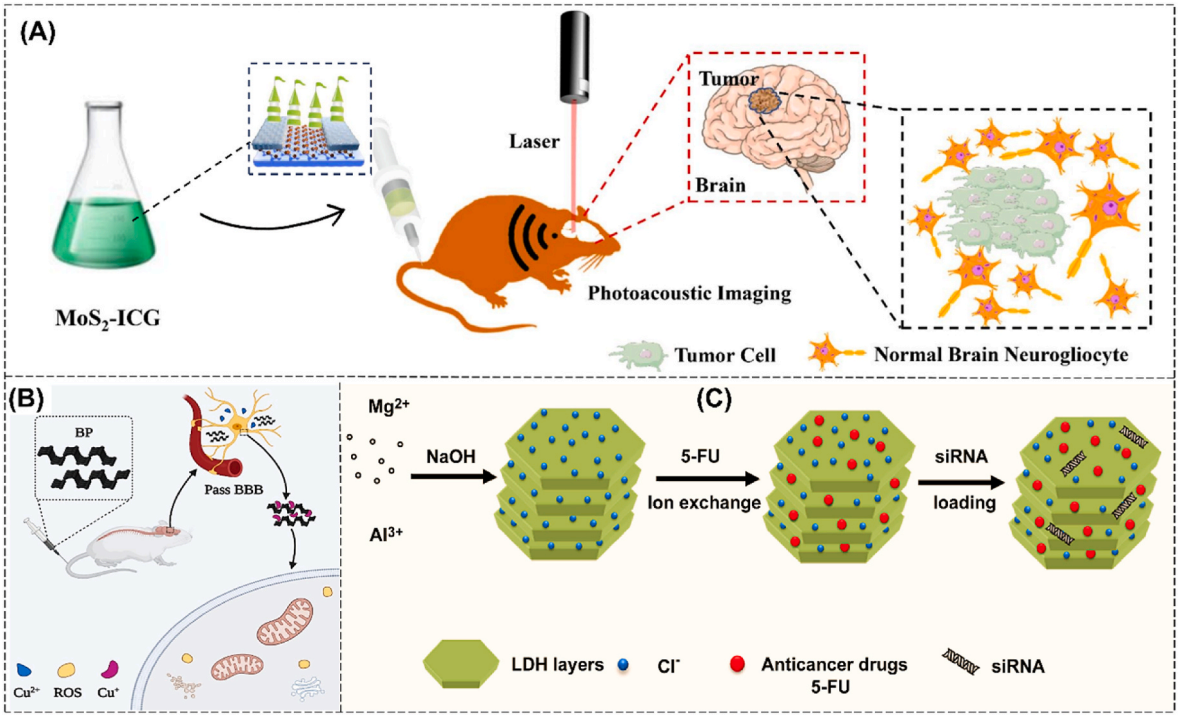

Fig. 14. **(A)** Schematic diagram for *in vivo* photoacoustic imaging of *in situ* glioma in mice, signifying the high sensitivity for visualization of deep glioma with the help of indocyanine green modified MoS_2 nanosheets. **(B)** After passing the blood-brain barrier, BP nanosheets reduce the generation of ROS by selectively capturing Cu ions for neurodivergent treatments. Reproduced with permission [245]. Copyright © 2023, Springer Nature **(C)** LDH co-delivery system to load and deliver 5-fluorouracil and siRNA for combined chemo- and gene therapy. Reproduced with permission [248]. Copyright © 2014, Elsevier.

act as a neuroprotectant while selectively capturing Cu^{2+} in the human body against Cu^{2+}-induced neurotoxicity. Such nano-delivery systems make BP nanosheets a promising therapeutic alternative for neuro-related diseases (see Fig. 14 (B)) [245]. Similarly, LDHs can be used as a nanocarrier to deliver a common chemotherapeutic drug (vepesid, etoposide, VP16) with a significant reduction in its side effects and improved drug uptake by the infected cells. The common side effects of VP16 are hair loss, liver damage, leukopenia, and gastrointestinal problems [247]. However, the research of advanced 2D NMs as a drug delivery system is still in its infancy. These NMs have demonstrated functional properties (such as biodegradability and biocompatibility), making them a better vehicle to load and deliver small molecules. However, they require them to evaluate further their interaction with larger molecules, proteins, and cells to widen their applications. Besides loading small molecules and anticancer drugs, LDHs can also be exploited to load small interfering RNAs (siRNAs) for gene therapy, and immunological adjuvants for tumor immunotherapy. LDHs were employed simultaneously to deliver siRNA and 5-fluorouracil (anticancer drug) for combined chemo- and gene therapy. This strategy utilized an anion exchange capacity of LDHs by inserting 5- fluorouracil into its interlayer spacing and loading siRNAs on the surface of LDHs and exhibited significantly enhanced therapeutic antitumor efficacy. A schematic diagram of the LDH co-delivery system to load and deliver 5-fluorouracil and siRNA is shown in Fig. 14 (C) [248].

Apart from the discussed 2D NMs, many other 2D NMs contributed to neural regeneration and repair, such as 2D metal-organic framework (MOF) and self-assembled 2D materials. The 2D MOF nanosheets demonstrated high purity, tuned surface area, ultrathin layer thickness, unlimited exposed unsaturated metal sites, and adjustable chemical composition compared with their 3D counterparts. Moreover, their drug-loading capacity makes them favorable to be used in drug delivery and tissue engineering. Meanwhile, self-assembled 2D materials showed unique physical and chemical properties, offering flexible nanostructures and biofunctions compared to inorganic 2D materials, promoting their applications in neural regeneration and repair [238]. Natural and synthetic polymers have been extensively tested and have numerous applications in biomedical engineering owing to their biocompatible nature. However, these polymers require specific physiochemical modifications to perform at the target site with effective, stable delivery. Poly (lactic-co-glycolic) acid and poly (lactic acid) showed topical and transdermal delivery in the presence of an anti-inflammatory model drug (Betamethasone valerate, BV). These nanofilms showed a higher adhesiveness and maximum skin concentration after application than commercial ointments. These nanofilms can incorporate and release therapeutic levels of the model drug without affecting adhesiveness or breathability [238,249].

3.3.3. Challenges in nanotoxicity data availability

In this section, we discussed the biomedical significance of dysbiosis and cellular toxicity and evaluated the availability of nanotoxicity data and its influential transformation into valuable information. The millions of small molecules (or nanoscale organic and inorganic materials) and their associated biological activities data allow molecular dynamic studies based on machine learning, which can significantly reduce research times in drug discovery or designing and equipment costs [250]. One of the major challenges associated with nanotoxicity data is NMs' breakthrough in the field of biology, which depends on multiple steps (synthesis, characterization, and application of NMs). Moreover, the quality of nanotoxicity data for NMs is also affected by other problems, including a lack of universal standard experimental protocols and reporting formats. In addition, the quality and effective quantity of most current nanotoxicity data are insufficient for generating machine learning (ML) models, and their effectual exploitation seems difficult. The limitations associated with NMs' synthesis, characterization, and application tests are the major causes behind the lack of ML modeling of nanotoxicity data. However, the quantitative relationships between nanostructures, physicochemical properties, and nanotoxicity can be established conveniently using ML. The key parameters contributing to their nanotoxicity are size, shape, hydrophobicity, and surface charge [41,251].

The generation of nanotoxicity data mainly comes from two sources: experiments and simulations. Experimental nanotoxicity data can capture critical nano-bio interaction outcomes and provide authentic NMs characterization relevant to the experimental conditions. However, most current nanotoxicity data are generated from *in vitro* studies (oxidative stress, cytotoxicity, and apoptosis) and are cheaper, faster, and more efficient for evaluating NMs. The collection, curation, and display of nanotoxicity data is a prerequisite and can provide useful information on NMs' environmental fate and their pharmacological behavior, such as adsorption, transformation, and degradation [252]. To improve the data quality, researchers are required to perform rigorous characterization of NMs to offer completeness of nanotoxicity data. However, it cannot be applied to the current status while considering the completeness of available nanotoxicity data [253,254]. For example, retrieving the antibacterial studies based on 200 research papers from a large pool of scientific data can be used to consider the completeness of nanotoxicity data. However, these selected data lacked major key parameters, including size, shape, surface charge exposure time, temperature, and dosage, which directly correspond to the main steps of the research study (physicochemical characterization and optimization of experimental conditions). Whereas missing data (i.e., data incompleteness) is a common problem across all the research fields. Rigorous characterizations of NMs are required to ensure the quality of NMs and the reliability of nanotoxicity data. Moreover, a preliminary standard for reporting nanotoxicity data has been proposed lately, suggesting that the displayed data should include three major components, i.e., material characterization, biological characterization, and comprehensive experimental protocols [251]. Nanotoxicity data availability can be improved with precise nanotoxicity quantification, which typically requires several crucial study objectives, such as determining quantitative experimental indicators, minimum toxicity value, and toxicity test method [254].

The curation and collection of available nanotoxicity data is quite important as it will be the major source of nanotoxicity data stored in the form of scientific publications, dissertations, patents, and conference reports. On the other hand, formal curation is not being done correctly for the large amount of nanotoxicity data that has been generated. In such a situation, molecular stimulation can help bridge the existing gap between the nanotoxicity data pool and a mechanistic perception of nanotoxicology by using various ML approaches [255]. Complex biological systems and their specific responses to NMs can cause desired and unpredictable cascading events, where NMs in biological systems interact simultaneously or sequentially with multiple molecules at once. This level of complexity has yet to be attained by molecular simulations, where stimulations of NMs' interaction with single molecules should be improved and require further simulations of NMs' interactions with multiple molecules to visualize mechanistic descriptions of interacting multiple molecules at once. By adding to the existing challenges, data scientists may be required to dissolve the incongruent hinders that limit the direct quantitative comparison between simulation results and experimental measurements, such as simulations' length and time scales, which are much smaller than those given in actual experiments [256].

4. Conclusion and future perspectives

In recent times, traditional antibiotics have greatly reduced the antibacterial developments and their application in medicine due to the increasing dilemma of multi-drug resistance among different bacterial communities. Fortuitously, various emerging 2D NMs proved promising potential against multi-drug resistance and biocompatible opportunities in addressing antibacterial issues. In this review, we systematically

reported the research developments of multipurpose 2D NMs, from materials classification to antibacterial mechanisms and the significant impact of their physiochemical properties on antibacterial applications. 2D NMs, including graphene, have demonstrated advanced features (effective surface area, better stability, suitable biosafety) that make them worthy candidates in antibacterial strategies [257]. The existing antibacterial mechanisms for 2D NMs mostly involve physical destruction, oxidative stress, photo-induced cellular and intracellular damage, metal ions release, and multi-mode synergized antibacterial approaches. Among these, synergetic antibacterial strategies are the most efficacious bactericidal methods that primarily involve photo-induced, particularly photocatalytic antibacterial characteristics, which have drawn much attention recently [258]. Moreover, we have divided 2D NMs into three to four categories to explain their recent antibacterial advancements: metal-based, nitride-based, graphene-based, and other 2D NMs (MXenes, BP, LDHs). They hold great promise in various biomedical applications, including diagnosis, wound healing, drug delivery, water disinfection, and antibacterial studies. However, before their clinical application in antibacterial treatments, it is crucial to evaluate their biosafety systematically. While some studies have explored biosafety aspects, there is still insufficient evidence to address all concerns related to 2D NMs and their chemical origins. Additionally, their long-term biological impacts remain uncertain. To enhance the biological activity of 2D NMs, several key factors are necessary for their designing and fabrication, such as optimization of surface functionalization for better biodegradability and targeted antibacterial capabilities, reduction in long-term toxicity, and understanding of clearance pathways while minimizing cytotoxicity. However, detailed investigations are

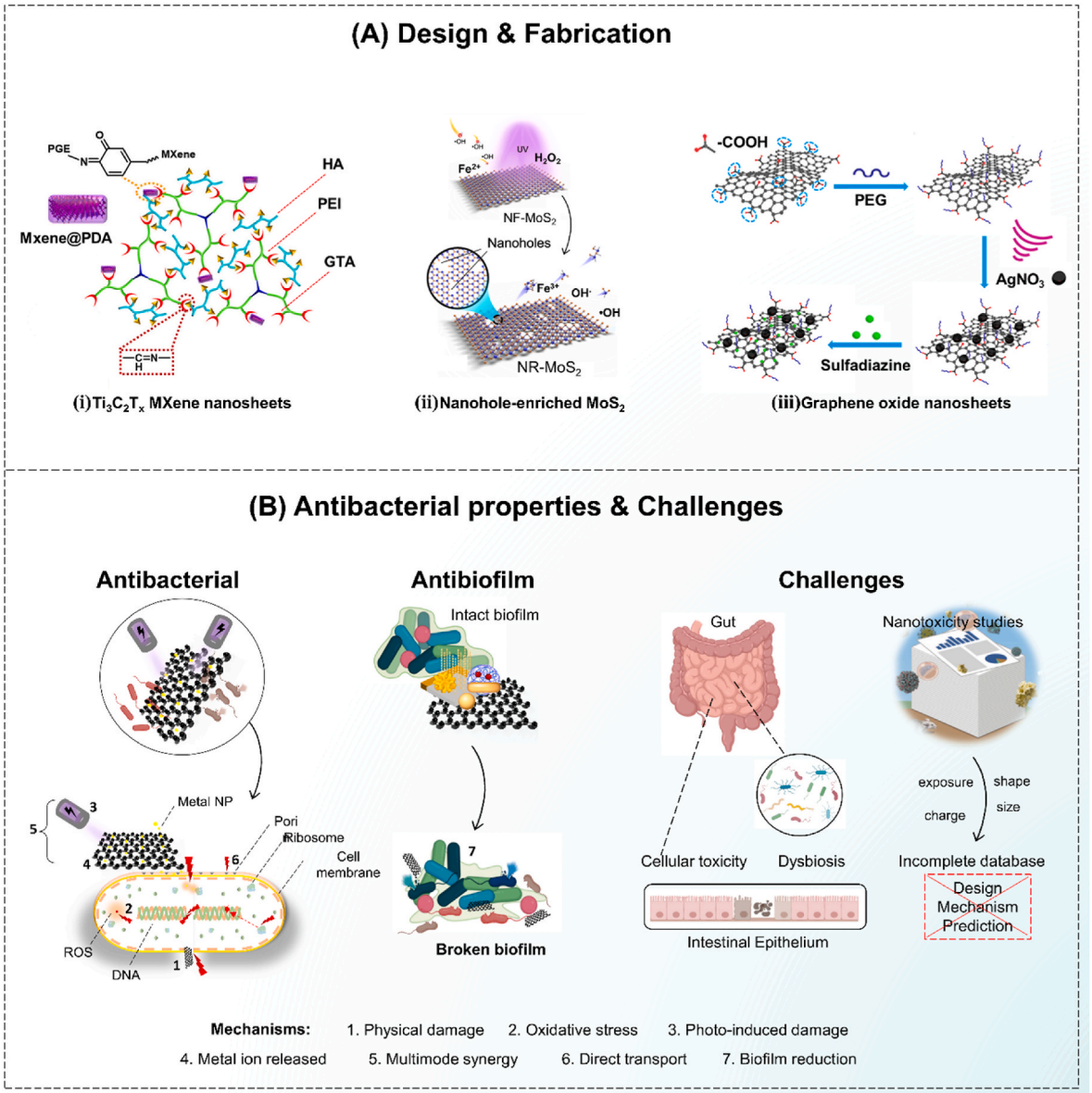

Fig. 15. Illustrated summary of 2D NMs and their antibacterial activities: **(A)** Design and fabrication, Functionalization, and fabrication of various 2D NMs with other chemicals and nanoparticles such as **(i)** 2D $Ti_3C_2T_x$ MXene nanosheets against MDR bacteria (where HA, hyaluronic acid; PEI, branched polyethyleneimine; GTA, glycerol triacrylate; MXene@PDA, PDA-decorated MXene), Reproduced with permission. Copyright © 2021, American Chemical Society [109] Copyright Year, Publisher **(ii)** Fabrication of nanohole-enriched MoS_2 nanosheets and their application against MDR bacteria and biofilm, Reproduced with permission [104]. Copyright © 2021, Springer Nature **(iii)** Fabrication of surface-modified graphene oxide nanosheets with AgNPs and sulfadiazine (SD) for proficient antibacterial performance, Reproduced with permission [79]. Copyright © 2020, Springer Nature **(B)** Antibacterial properties and challenges of 2D NMs, showing fundamental antibacterial mechanisms and their critical role in dysbiosis and cellular nanotoxicity with the existence of incomplete and missing data from nanotoxicity databases. Created with BioRender.com. Nanotoxicity studies were taken and Reproduced with permission [251]. Copyright © 2023, American Chemical Society.

imperative to address these unresolved biosafety issues. A detailed summary of this review content is illustrated in Fig. 15, which includes the innovative ways of NMs' fabrication and their application as practical tools while considering their pitfall nature.

Besides, a comprehensive understanding of the nano-bio interactions between 2D NMs and bacteria and their interrelated antibacterial mechanisms is needed. The physicochemical properties of these NMs, such as size, shape, and surface functionalization, significantly affect their antibacterial efficacy, necessitating systematic studies to elucidate these relationships. Moreover, research should focus on finding optimal therapeutic antibacterial approaches, especially in the case of deep-skin infections. In the realm of clinical applicability, 2D NMs offer promising prospects for tissue repair, regenerative medicine, and treatment of various medical conditions. However, further medical investigations are required to ensure their safe and effective use. Also, there is potential for these NMs to be developed into antifungal and antiviral agents, but significant efforts are needed to facilitate their clinical translation. Moreover, NM's design is one of the prime factors for avoiding the evolution of antimicrobial resistance. Antibacterial and antimicrobial NMs could be designed in a specific way without triggering the evolution of resistance mechanisms, such as the fabrication of engineered NMs with specific structural attributes (catalysis of bacterial metabolites, structural disruption of biomolecules, and interaction with bacterial membrane constituents *via* electrostatic forces) to differentiate various ways of nano-microbe interactions, precise antibacterial elimination by specific surface functionalization using other biomolecules or ligands and their sustainable release *via* stimuli-responsive interaction (temperature, pH, light), and advanced surface coating of NMs to avoid metal ion release and unrequired biological interactions while applying *in vivo* testing. Current computational simulations have shown the capability to visualize different nanotoxicological events occurring inside the cells, whether it is associated with nano-bio interfacial interactions (cell membranes, protein adsorption) or involve the determination of chemical forms of disintegrated NMs as a result of ROS generation or casual chemical transformation. Advanced computers combined with artificial intelligence can enhance the potential of computational simulations and help design and predict the mechanism of multiple antibacterial mechanisms and their interactions with cells. These simulations can complement experimental research and provide valuable insights into the antibacterial effects of 2D NMs *via* a combination of computational simulation and theoretical calculation. Conclusively, the recent progress in 2D antibacterial NMs is bound to provide new insights into exploring the unspecified antibacterial mechanisms and addressing the present issues. However, extensive research established 2D NMs as excellent antibacterial agents, yet their clinical applications are occasional. Therefore, to realize their practical significance, we must emphasize the important issues in the future.

Lastly, to reduce the exposure sources of nanomaterials in research laboratories or industrial manufacturing processes for bulk preparation, water reservoirs with heavy metals, plants, and animals we need to understand their exposure routes and their unintended release from consumer products or waste, which necessitates comprehensive risk management strategies. We know that nanomaterial exposure can be minimized through engineering controls, personal protective equipment in labs and industries such as gloves, respirators, lab coats, and goggles to minimize direct contact with nanomaterials and prevent inhalation or skin exposure, enforcing regulations and fostering education on safe handling practices.

Data availability statement

No data is available for this publication.

Ethics approval and consent to participate

Not applicable.

Declaration of competing interest

The authors declare the following personal relationships which may be considered as potential competing interests: Muhammad Ovais is currently employed by BGI Shenzhen.

CRediT authorship contribution statement

Saima Hameed: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Sumaira Sharif:** Writing – review & editing. **Muhammad Ovais:** Writing – review & editing. **Hai Xiong:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

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Abbreviations and vocabulary

2D NMs	two-dimensional nanomaterials
NPs	nanoparticles
NCs	nanoclusters
MDR	Multidrug-resistant
HGT	horizontal gene transfer (transfer of genetic material between different genomes)
ARGs	antimicrobial resistance genes
QS	quorum-sensing
EPS	extracellular polymeric substances
CVD	chemical vapor deposition
ROS	reactive oxygen species
GO	graphene oxide
(g-C_3N_4)	graphitic carbon nitride
TMD	transition metal dichalcogenides
MXenes	transition metal carbides, and nitrides
HA	hyaluronic acid
PEI	branched polyethyleneimine
GTA	glycerol triacrylate
MXene@PDA	PDA-decorated MXene
LDHs	layered double hydroxides
BP	black phosphorus
h-BN/hBN	hexagonal boron nitride
PG	Pristine graphene
GO	graphene oxide
rGO	reduced GO
SD	sulfadiazine
Ag	silver
Bi	bismuth
Au	gold
Pt	platinum
Pd	palladium
Cr	chromium
HAS	hybrid antibacterial system
LDPE	low-density polyethylene
PP	polypropylene
QAC	quaternary ammonium compounds
PDA	polydopamine
BSA	bovine serum albumin
Lap	laponite
PTT	photothermal therapy
PDT	photodynamic therapy
NIR	Near-infrared
Bi_2S_3	Bismuth sulfide

MoS_2	Molybdenum disulfide
BNN6	N,N′-di-sec-butyl-N,N′-dinitroso-1,4-phenylenediamine
CuS	Copper sulfide (general formula Cu_xS_y)
Sb_2Se_3	antimony selenide
CoNWs	cobalt nanowires
TiO_2	Titanium dioxide
Bi_2WO_6	bismuth tungstate
ZnO	Zinc Oxide
g-C_3N_4 NS/RGO	graphitic carbon nitride nanosheets/reduced graphene oxide/
V_2O_5/$BiVO_4$	Vanadium pentoxide/bismuth vanadate
G-WO_3	graphene-tungsten oxide
Bi_2MoO_6	Bi-coordinated nanocomposite of molybdenum oxide phase
O_2	oxygen
H_2O	water
$\cdot O_2^-$	superoxide ion
·OH	hydroxyl radical/hydroxide ion
H_2O_2	hydrogen peroxide
Nb_2C	niobium carbide
CeO_2	cerium oxide
SiO_2	silicon dioxide
WS_2	tungsten disulfides
NR	nano-enriched
NF	nano-free
MoS_2	molybdenum disulfide
Cys	cysteine
PDDA	poly(dimethyldiallylammonium chloride)
ATP	adenosine triphosphate
SDS-PAGE	sodium dodecyl-sulfate-polyacrylamide gel electrophoresis
GIT	gastrointestinal tract
GM	gut microbiota/microbiome
IBD	inflammatory bowel disease
SI	small intestine
LI	large intestine
ML	machine learning
Ti-SA_4@BPs	BP nanosheets loaded with titanium aminobenzenesulfanato complexes
Pd@OH-BNNS	h-BN nanosheets loaded with palladium nanoparticles

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