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Review Article

Surface Disinfections: Present and Future

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The propagation of antibiotic resistance increases the chances of major infections for patients during hospitalization and the spread of health related diseases. Therefore finding new and effective solutions to prevent the proliferation of pathogenic microorganisms is critical, in order to protect hospital environment, such as the surfaces of biomedical devices. Modern nanotechnology has proven to be an effective countermeasure to tackle the threat of infections. On this note, recent scientific breakthroughs have demonstrated that antimicrobial nanomaterials are effective in preventing pathogens from developing resistance. Despite the ability to destroy a great deal of bacteria and control the outbreak of infections, nanomaterials present many other advantages. Moreover, it is unlikely for nanomaterials to develop resistance due to their multiple and simultaneous bactericidal mechanisms. In recent years, science has explored more complex antimicrobial coatings and nanomaterials based on graphene have shown great potential in antibacterial treatment. The purpose of this article is to deepen the discussion on the threat of infections related to surface disinfection and to assess the state of the art and potential solutions, with specific focus on disinfection procedures using nanomaterials.

1. Introduction

One of the most important routine practices in dental units is the chemical disinfection of surfaces and instruments for infection control. When it comes to selecting disinfectants, it is crucial to take into account several aspects, such as timing, disinfection methods, the risks posed by using germicides, and factors affecting their effectiveness [1]. Chemical disinfectants are essentially active substances in aqueous solutions, engaged in different forms according to their final purpose: immersion, sterilization, disinfection, and decontamination of medical equipment, such as sprays to disinfect the surfaces. Sterilizing and disinfectant products are classified in three levels: high, intermediate, and low, according to the pathogens they are able to kill [2–5]. However, it should be remembered that sterilization with sterilizing by means of chemical products, for critical and semicritical items, is always the second choice in terms of process to be implemented on thermosensitive material (for which sterilizing with heat is not advised). The correct use of disinfectants should take into account the fact that the biocide property is influenced by the concentration, time of contact, and potential traces of interfering material or substances (e.g., organic fluids, soap, metallic ions, and pH) [6–8]. Ideally, the perfect disinfectant should possess a complete antimicrobial spectrum, act rapidly and persistently, lack toxicity to humans and the environment, be compatible with the material to treat, be chemically stable, and be economical and easy to use. Actually, no product meets all these requirements; therefore, we need to find the best possible compromise to achieve the ideal result, minimizing the disadvantages related to their use [9]. In order to reach this target, all the details and information written in the technical sheet and safety documents provided by the manufacturer must be carefully analysed. All the chemical and physical features are listed in this documentation, and there are instructions for the correct usage and disposal in order to prevent the equipment from being damaged and protect the worker's safety at the same time. Once a disinfectant passes the cell wall, it is able to act on the pathogen organism through coagulation mechanisms and protein oxidation of microbial cells and by denaturalizing bacterial enzymes. If these substances are

compatible, they can be used in association and produce a synergetic action that enhances the technical features of the final product [10]. There are several compounds that can be divided into groups according to the basic compound they originate from. There is a wide range of disinfectants available on the market, including halogen compounds like sodium hypochlorite, alcohols, peroxygen compounds like hydrogen peroxide, and aldehydes like glutaraldehyde, all of which have a broad efficacy spectrum if used appropriately. Other types of disinfectants such as phenols, quaternary ammonium compounds, and biguanides (including chlorhexidine) are mostly ineffective with nonenveloped viruses and bacterial spores, and most of them have limited ability to kill mycobacteria [11, 12]. Chemical products like disinfectant, germicide, microbiocide, and biocide are often confused, and many of their synonyms imply a broad spectrum of efficiency against multiple microbial pathogens. Nevertheless, a certain product may potentially be effective only against one class of microorganism. The main target of the disinfection process is to interrupt the transmission of pathogens from an infected subject to a susceptible host. Chemical disinfection is generally limited to the use of liquid germicides on equipment and environmental surfaces. Surface contamination of a pathogen shed into the environment can occur directly or by means of settled aerosols. Environmental factors such as temperature, relative humidity, the specific nature of the pathogen, and its suspending medium determine the survival of these organisms. Their lifespan ranges from a few minutes to weeks and even months. During this period of time, contact with the contaminated item can lead to direct inoculation of a susceptible host or, more commonly, contamination of another vehicle, like the hands, through which indirect inoculation occurs. Disinfectants may prove effective in preventing the survival of pathogens and their transfer to subordinate vehicles and ultimately to susceptible hosts [13]. Nevertheless, chemical disinfection should only be employed when heat sterilization is not possible. In some cases however, it is necessary to perform a high-level chemical disinfection of the medical instruments after each use [14]. Evaluating the patients' and staff's risk exposure to potentially contaminated surfaces (directly or from settled aerosols), such as frequently contacted surfaces, is crucial to determining the need to disinfect environmental surfaces. There are three basic principles, of equal importance, that must be followed to achieve a successful result. It is important to choose a good product since poor disinfectants will fail even if properly applied. Applying the correct protocol for the selected product is also very important because even using a good product may prove ineffective if the method of application is not good contact with the contaminated surface/s. Disinfection presents a duality within its nature. A disinfectant is a powerful substance engineered to kill and can pose a serious threat if used frequently or improperly [15]. Resistance to germicides is extremely rare and, yet, lately there has been significant interest in the fact that there are some mechanisms of bacterial resistance that overlap between germicides and antibiotics, which in either way are bacterial toxins. Thus, the exposure to sublethal concentrations of germicides may trigger antibiotic resistance.

2. Antibiotic Resistance

At the beginning of the twentieth century, infectious diseases were the main cause of death in the world and only with the introduction of antibiotics was it possible to reduce the mortality rate caused by them. These molecules revolutionized modern medicine, saving millions of lives and containing many serious infections. They were considered as "wonder drugs" because of their nature: these are chemical compounds produced by actinomycetes, fungi, or bacteria capable of acting on other microorganisms inhibiting growth (bacteriostatic effect) or killing them (bactericidal effect). Antibiotics have many modes of action, such as inhibiting the synthesis of a bacterial cell wall, biosynthesis of proteins, RNA, DNA, and disrupting membrane organization. The use of antibiotics began with the commercial production of penicillin at the end of 1940 and was a great success until the development of newer more effective molecules in the 1980s [16]. In the last decade, these medicines remained one of the most commonly prescribed classes of drugs, with 70 billion of doses consumed [17]. An unforeseen aspect, after discovery of antibiotics, was their widespread use, abuse, and misuse in various forms and in different parts of the world. The level of antibiotic-resistant infections was found to be strongly linked to the increase of antibiotic consumption [18]. Over the next five decades since the introduction of these drugs, there has been an unprecedented natural selection in evolutionary history that had led to an increasing number of resistant strains [19]. The discovery of new molecules and the chemical modification of existing ones, however, did not overcome the problem. In addition, the development of antimicrobial drugs gave a low return on investment, so since the late 1980s, it was possible to observe a gap in the production of antimicrobials, which was abandoned in favour of medicines that allowed for a greater profit. This had further contributed to the current crisis in the fight against drug-resistant pathogens [20]. Antibiotic-resistant organisms are known as "superbugs," which are no longer sensitive to antibiotic and continue to multiply in its presence. The World Health Organization estimated 25,000 deaths due to drug-resistant infections every year only in Europe, while in the United States, more than 63,000 patients die every year from hospital-acquired bacterial infections that cost about $35 billion to society, causing discomforts also economically [16]. The first serious clinical threat in fighting infectious diseases occurred with Enterococcus Vancomycin-resistant strains (VRE), which possess intrinsic resistance to many of the commonly used antibiotics and, perhaps more importantly, the ability to gain resistance to many antibiotics present on the market [21]. Among other things, recent American studies have found that more than 40% of *Staphylococcus aureus* strains collected in hospitals resulted in being resistant to methicillin (strains of *S. aureus* methicillin-resistant, MRSA) and some of them also to vancomycin (multidrug-resistance), unfortunately a recent molecule [22]. Antibiotic resistance is a natural process that occurs via gene level mutation and for this reason it is impossible to overcome or prevent its development. Indeed, a simple selective pressure and an imperfect chromosome replication lead to acquiring one or more mutations in the

protein or gene target of the antibiotic that prevents binding (transforming the target into insensitive variants) [23]. The new antibiotic capability by bacteria is acquired de novo by genetic mutations or obtained from an external source. In fact bacteria are able to transfer and interchange genetic material directly between each other by transferring plasmids. This mechanism is known as horizontal gene transfer (HGT) and it is common among bacteria, even among those that are phylogenetically distant [24]. It is considered as one of the most important reasons in the evolution of drug resistance that acts in association with natural selection. Resistant bacteria can also spread in the environment thanks to the presence of human and animal excrements, as in the case of farms and wastewaters, which are able to convey such microorganisms, spreading them elsewhere. Antibiotic-resistant species and traces of drugs can pass through the intestines of humans and animals, contaminating subsequently waters and soils: in fact, rivers and lands cultivated with the use of organic fertilizers coming from animals fed with antibiotics would be able to induce the proliferation of bacteria resistant to them [25]. Bacteria that are not annihilated by antibiotics resist their action and continue to multiply, creating increasingly resistant strains which, after being fortified, may reach our organism by passing through the aquifers or the food grown on contaminated soils. Nowadays water resources are among the major sources of hyperresistant bacteria [26, 27]. Resistant bacteria are involved in the high incidence of healthcare-acquired infections (HAIs), recognized as critical emergence in hospitals and clinics around the world. Infected patients disseminate and release many multidrug-resistant Gram-negative and Gram-positive species to other ones and to healthy people: such bacteria share the ability to survive on various hospital surfaces for long periods and for this reason they are difficult to eradicate by cleaning and chemical disinfection. From surfaces, pathogens may infect patients by direct contact or indirectly, by means of the hands of medicals and healthcare workers. Thus cleaning and surface disinfection are very important in order to limit their transfer and reduce their diffusion [28]. The efficacy of cleaning practices can be affected by many factors, which can compromise the disinfectant action itself. Many studies report that different types of surfaces prepossess the bacteria removal properties [29]. Besides, an inadequate use of disinfectants and incorrect contact times result in low surface disinfection. If manufacturer's instructions are not followed, contaminations of sanitiser solutions may also occur worsening the situation [30]. In addition, the use of disinfectant wipes with a poor germicide activity and composed of a considerable quantity of cellulose or cotton (which can sequestrate quaternary ammonium molecules) may decrease their efficaciousness and serve conversely as means for microbes [31, 32]. New disinfectants, antimicrobial surfaces, automated dispersal systems, UV irradiation, hydrogen peroxide decontamination, and steam treatments could represent novel overtures in contrast with the traditional and often ineffective cleaning methods; however, they are more expensive than usual ones [33].

So with the aim of preventing and controlling infectious diseases caused by multidrug-resistant bacteria, we need continually to develop new strategies and therapeutic innovations to contribute to the fight against antibiotic resistance. For this reason, during the last years, a great importance was given to the research of novel substances and compounds with antimicrobial activity. In this regard, nanomaterials and nanoscience seem to be a good solution in solving this public health problem.

3. Graphene-Based Nanomaterials as Novel Antimicrobial Drugs

A new perspective in the treatment of bacterial infections is offered by the use of nanomaterials and nanoparticles as novel and nontraditional antibacterial agents [34–37]. In particular, more recently, graphene has been proposed as a novel antimicrobial material. Graphene is a single-layer sheet of carbon atoms that are packed closely in a two-dimensional (2D) honeycomb lattice. It has unique physicochemical properties including a high surface area, extraordinary electrical and thermal conductivity, and strong mechanical strength [38–40]. Graphene and its derivatives (like graphene nanoplatelets, multilayer graphene flakes, graphene oxide, and reduced graphene oxide) are considered graphene-based nanomaterials (GFNs) and have been studied extensively in material science, chemistry, biotechnology, and nanomedicine for a wide range of applications including biosensing/bioimaging, disease diagnostics, drug delivery, and photothermal therapy [41–46]. GFNs vary in shape, size, surface area, layer number, lateral dimensions, surface chemistry, stiffness, defect density or quality of the individual graphene sheets, and purity; and all these properties significantly influence the interaction of GFNs with biological systems [47]. Generally, GFNs with small size, sharp edges, and rough surfaces easily internalize into the cell as compared to larger, smooth GFNs [48]. GFNs, particularly monolayer graphene, have the theoretical maximum surface area because every atom lies on the surface, providing an extremely high capacity for drug delivery [49, 50]. In particular, more recently, graphene has been proposed as a novel antimicrobial material, with a strong cytotoxic effect on both Gram-positive and Gram-negative bacteria and fungi [48–52] but a very low cytotoxic effect on human cells and animal models [53, 54]. In general, with respect to carbon nanotubes, graphene-based nanomaterials are preferable due to the lower production cost and ease of manipulation. With reference to antimicrobial application, graphene-based materials are preferred with respect to carbon nanotube due to their better efficiency against bacteria and ease of use [51]. Reports indicate that GFNs exert cytotoxicity in both in vitro and in vivo studies in various types of bacteria, mammalian cells, and animal models [53]. Among them, graphene oxide (GO) has good antibacterial effect against *Pseudomonas aeruginosa* and *Staphylococcus aureus* compared to benzalkonium chloride one, a common surface disinfectant. Reduced GO (rGO) can be also used as an antibacterial surface when it is activated by solar near-infrared irradiation that gives it the ability to kill the majority of airborne bacteria on contact, proving to be a very efficient coating nanomaterial [55]. It has been shown that these nanostructures also have

a remarkable antimicrobial activity against some multidrug-resistant bacteria such as *Klebsiella pneumoniae*, *Escherichia coli*, and *P. aeruginosa* [56]. Most published studies have evaluated graphene oxide (GO) and reduced GO (rGO) due to their better solubility/dispersibility/stability in water and under physiological conditions compared to other GFNs. However, it is demonstrated that GO and rGO induce formation of reactive oxygen species (ROS), which are representative of an induced oxidative stress on the cell. On the contrary, it is demonstrated that multilayer graphene flakes and graphene nanoplatelets have cytotoxic effect on bacteria cell but without induction of ROS [53]. Like in other types of nanocompound, the antimicrobial effect of graphene derivatives is defined by mechanical interactions damaging cell walls and by its chemical oxidation that lead to the generation of reactive oxygen species (ROS) [57]. Several works report the development and production of graphene-based nanomaterials, zinc-oxide nanostructures, and zinc-oxide-decorated graphene nanoplatelets [58, 59] for use as severe antibacterial and antibiofilm agents [60–62] (Figure 1) but without exerting relevant cytotoxic effect on human cells in vitro. Physical interaction between nanomaterial and bacterial cell leads to a direct damage of the cell wall, whereas chemical interaction leads primarily to formation of reactive oxygen species (ROS), which are representative of an induced oxidative stress on the cell. In particular, this developed nanomaterial does not induce ROS production on the cell, and for this reason it can produce a cytotoxic effect on bacteria and fungi but not on human cells and animal models [60]. In general, the antibacterial action of nanomaterials and nanoparticles involves both physical and chemical effects. The interaction mechanisms that can be considered as the main cause of the antimicrobial effects of nanoparticles and graphene-based materials cannot be understood or expected without taking into consideration the fact that phenomena intrinsic to the nanoscale are governed by quantum effects and by the domain of the phenomena of surface and interface. It is known that nanostructures and nanoparticles are characterized by an increasing ratio between surface and volume atoms, as their size decreases. Therefore, nanoparticles are characterized by a much stronger surface interaction capability with other objects than microsized particles. In graphene, volume approaches zero and surface area infinity; it is thus understood that nanostructures have a much higher probability to get in touch and interact strongly with bacterial cell than microparticles [63]. There are several interaction mechanisms between nanomaterials and cell walls. Among them is bacterial wrapping: this mechanism characterizes the interaction, for example, of graphene nanoplatelets with bacteria, as shown in Figure 2. The D-nanostructure adheres to the bacterium surface and induces mechanical stress [64–66]. Several results report on the important role of 2D basal planes rather than edges in antimicrobial properties, in which completely flat Langmuir–Blodgett films act against bacterial cells having few contacts with sheet edges [67, 68]. This antimicrobial mechanism is a valuable alternative to biocide-releasing surfaces that uses antibiotics or silver, which are depleted from the surface over time [69]. Antimicrobial GFN surfaces also avoid the release of toxic biocides, relevant in the design of antimicrobial surfaces for environmental applications [70].

Another antimicrobial mechanism is based on membrane punctuation: nanostructures adhere to the cell wall and penetrate through the membrane with their sharp edges as shown in Figure 3. This mechanism is a characteristic of both D and 1D nanostructures (like GNPs and ZnO-NRs) [71] and it is particularly effective in case of GNPs decorated with ZnO-NRs (ZNGs), because the 2D shape of the supporting GNP enables the 1D ZnO-NRs decorating its surface to penetrate the cell wall [72]. Strategy to decorate GO nanosheets with structure-featured metal oxides was also addressed [73]. In fact, these nanomaterials took advantage of the large specific surface area and morphological features from graphene, but also introduced the bacterial activities of metal oxides simultaneously. Recently, the synthesis of Zn–CuO@GO nanosheets to apply as disinfectants has been carried out and demonstrated their activities to combat against multi-drug-resistant bacteria strains, such as a *E. coli* multidrug-resistant strain and a methicillin-resistant *S. aureus* strain [74]. The nanosheets, inhibiting bacterial growth via physical damage, function as effective antibacterial agents. In this way, possible genetic mutation and development of other drug-resistant mechanisms might not be applicable.

Graphene is also able to induce antiadhesion of the bacterial cells over the substrate for biofilm formation and it is particularly effective in order to prevent biofilm formation, as shown in Figure 4 [61].

The mechanism based on ROS generation does not seem to be activated by the nanostructures shown in Figure 1, because graphene is fully reduced and ZnO is a biocompatible material. This limits the cytotoxicity induced on human cells *in vitro* or on animal models like *Caenorhabditis elegans* [60] as it was observed in the case of GO [75–77].

Moreover, the development of bacterial resistance to such nanomaterials is improbable because of their multiple and simultaneous bactericidal mechanisms [78, 79]. Various medical devices such as synthetic fibers, venous catheters, and surgical instruments have already been treated with nanoantimicrobial coatings, using silver nanoparticles in order to fight nosocomial infections and subsequent bacterial resistance [80].

4. Conclusions

Health associated diseases are the main unwanted consequence of the spread of antibiotic resistance, so that, during hospitalization, the risk of serious infections for a patient is increasing. This suggests finding innovative and functional remedies to curb the propagation of pathogenic microorganisms from the surface of biomedical devices to the surrounding hospital environment. With this purpose, nowadays nanotechnology proves to be an excellent weapon in the struggle against infection. One of the recent efforts is the discovery of antimicrobial nanomaterials, so that pathogens may not be able to develop resistance. They have several advantages besides the ability to control infections and kill many bacteria: unlike the common antibiotics and detergents, nanoparticles are not toxic, stable for long periods, and

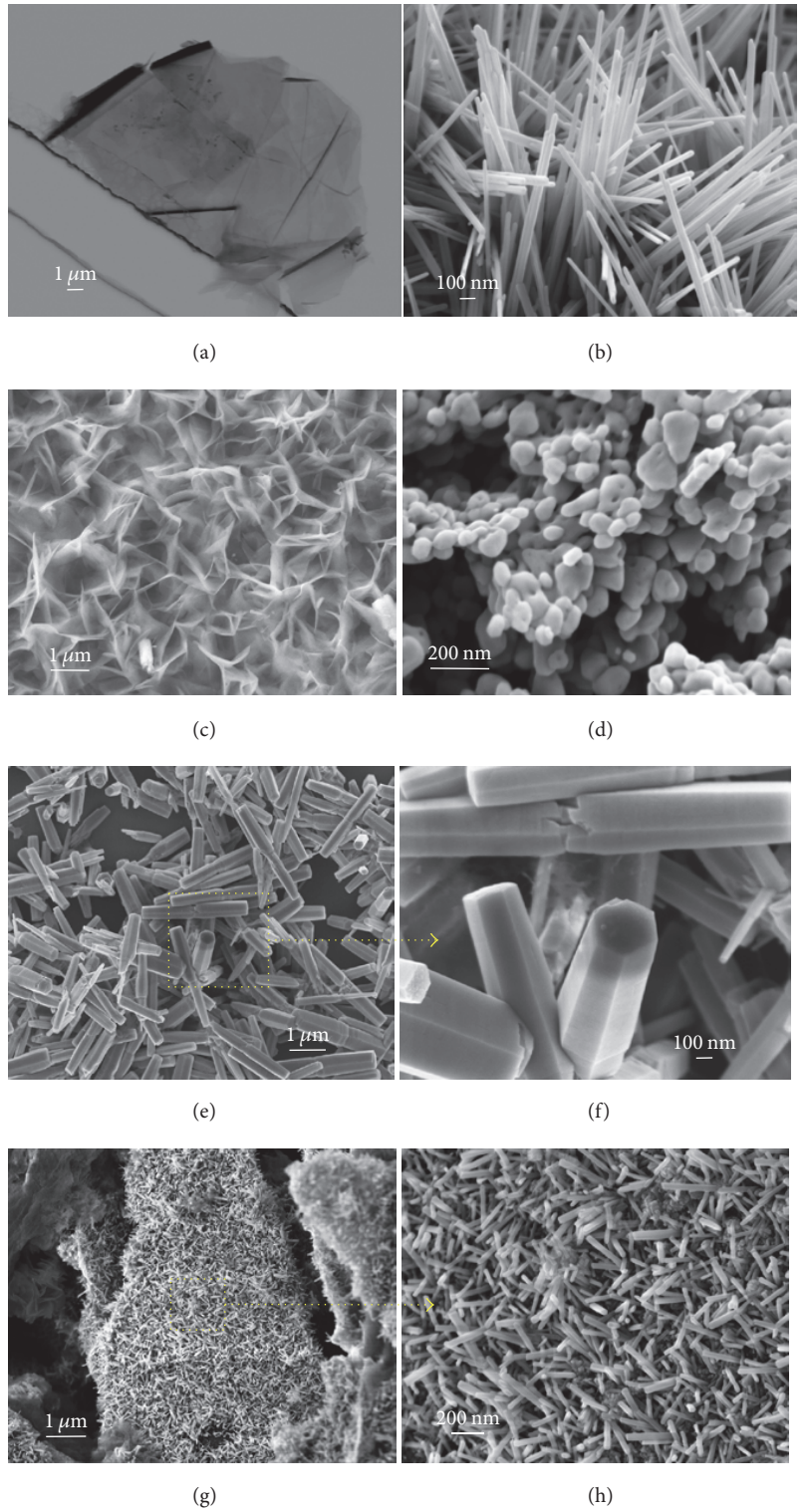
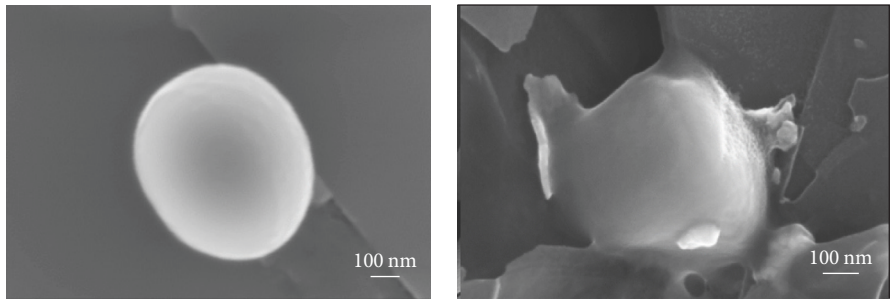


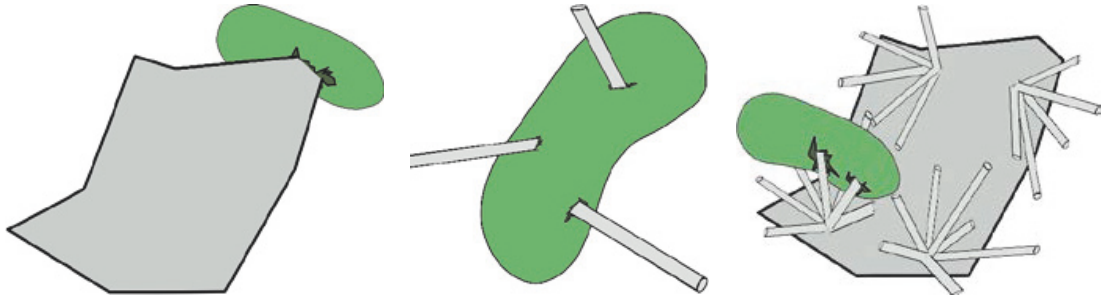
Figure 1: Original FE-SEM images showing the morphology of different nanomaterials produced at Sapienza-CNIS-DIAEE: (a) graphene nanoplatelets (GNPs); (b-c) zinc-oxide nanowalls (ZnO-NWs); (d) zinc-oxide nanoparticles (ZnO-NPs); (e-f) zinc-oxide microrods (ZnO-MRs); and (g-h) zinc-oxide-decorated GNPs (ZNGs).

simple to produce. Moreover, many chemical disinfectants have positive but above all negative aspects: there is no disinfectant with maximum effectiveness against a wide spectrum of pathogens; each case requires the choice of the most appropriate disinfectant, which depends on several factors, such as concentration, time of action, and the type of surface and microorganism. Many detergents could be contaminated by a wrong method of conservation and they could cause



(a) (b)

Figure 2: Original FE-SEM images of *Staphylococcus aureus* (a) wrapped by a GNP (b).



(a) (b) (c)

Figure 3: Mechanical damage of cell wall produced by sharp edges in 2D (a) or 1D (b) or hybrid 1D-2D (c) nanostructures.

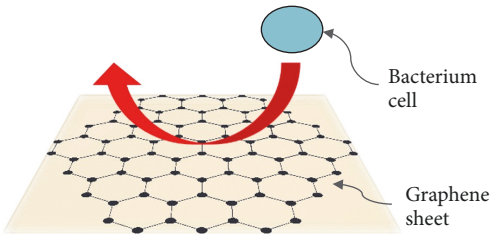


Figure 4: Inhibition of cell adhesion over a substrate induced by graphene.

hardening of plastics and a long-term deterioration of the treated materials. Therefore new generation nanomaterials may allow overcoming all these limitations and allow us to exploit only the positive aspects offered by these innovative applications. In the last years, more elaborated antimicrobial coatings were investigated and graphene-based nanomaterial emerged as promising antibacterial treatment. Layers of graphene-based nanomaterial can be employed as a novel surface coating resin or as a new fabrication material for medical devices and common objects touched by patients and hospital staff that require good disinfection and particular sanitation in the resistant-antibiotic era.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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