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22 *Current Topics in Medicinal Chemistry*, 2018, *18*, 22-41

FINAL

REVIEW ARTICLE

Learning from Nature: Bioinspired Strategies Towards Antimicrobial Nanostructured Systems

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ARTICLE HISTORY

Received: April 04, 2017
Revised: March 05, 2017
Accepted: November 22, 2017

DOI:
10.2174/1568026618666180206101129

Abstract: Microbial contamination still remains a major issue of the modern era, due to the widespread of drug-resistant pathogens. This has prompted researchers to come up with novel antimicrobial systems that could overcome antibiotic-resistance. In this context, nature can provide inestimable source of inspiration to design high-performance multifunctional materials with potent activity against drug-resistant pathogens. Actually, integrating the bio-inspired-approach with nanotechnology can provide cutting-edge solutions for drug-resistant infections. In this context, this review will examine recent advances in the development of bio-inspired antimicrobial nanostructures. Advantages of bioinspired approach to nanomaterials over conventional routes have been highlighted. Generally, bionspired synthesis can be carried out either by mimicking the functions of natural materials/structures or by mimicking the biological processes employed to produce substances or materials. The review provides an overview of both strategies as applied to the synthesis of inorganic, organic as well as hybrid nanostructures. Antimicrobial efficacy and biological properties of these systems have been highlighted. Antimicrobial and antibiofouling nanostructured surfaces are also discussed.

Keywords: Antimicrobial nanostructures, Bioinspired devices, Metal-based antimicrobial systems, Ceramic-based antimicrobial systems, Polymer-based antimicrobial systems, Hybrid antimicrobial systems, Anti-biofouling surfaces.

1. INTRODUCTION

Bacterial contamination is a major concern for food processing, biomedical as well as environmental fields. It usually causes higher costs of production of production and equipment maintenance, as well as negative public health and environmental impacts [1, 2].

Actually, infectious diseases [3], if not treated, can cause serious health issues and death [4]. The conventional antimicrobial treatment relies on antibiotics which are found to be toxic and narrow spectrum against drug resistant microbe [5].

The huge widespread of antimicrobial resistance to almost all available antibiotics [6] threatens the effective and sustainable treatment of infectious diseases, protracting illnesses and increasing mortality [7]. This prompts both science and medicine, to develop new active compounds towards pathogens, possibly by novel mechanisms of action that could impede the development of resistance in the microorganisms [8]. New strategies to tackle antimicrobial resistance include antimicrobial peptides (AMPs), phage therapy and phage enzymes, therapeutic antibodies, quorum sensing inhibitors and nanoparticles [9]. Indeed, effective solutions to drug resistant bacteria require the development of new strategies in the design of antimicrobial materials [10].

To this purpose, an attractive option is biomimicry-learning from nature's own designs and solutions to kill drug resistant pathogens by using bio-inspired strategy [11]. Nature is a valuable source of inspiration for the design and fabrication of high-performance synthetic materials and components.

Actually, Nature's remarkable ability to create systems with impressive and unique properties provides useful inspiration for the design and fabrication of high-performance synthetic materials and components [12]. These "bio-inspired" nanomaterials are of interest due to their peculiar properties, which have lined the way to many significant applications, ranging from climate control for buildings to electronics, from environmental to biomedical systems [13, 14]. With the recent strides made in the advancement of nanotechnology, many have envisioned this as an innovative component to provide cutting-edge solutions for drug-resistant pathogens [15].

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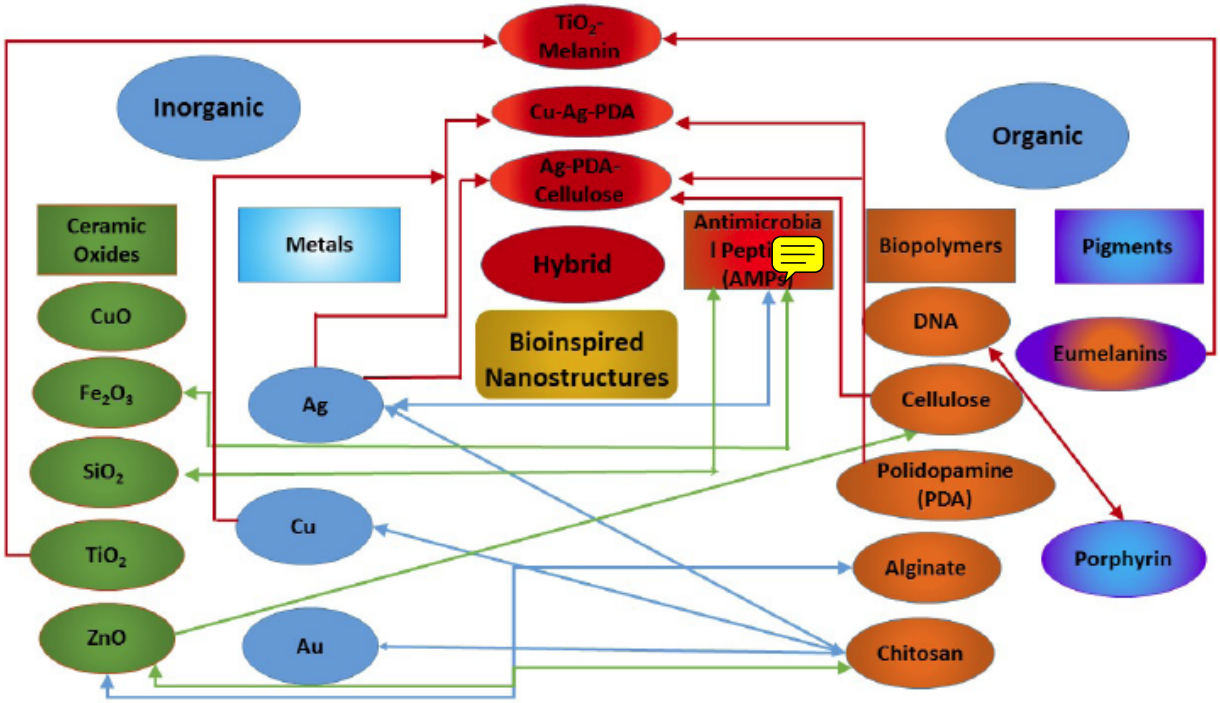

Fig. (1). An overview of bioinspired nanostructures as antimicrobial agents.

This review has been focused on the recent advances in the design and antimicrobial efficacy of bio-inspired nanomaterials. Aim of this review is elucidating the strategies that are currently adopted within the bio-inspired synthesis of antimicrobial systems:

- Exploiting natural sources as well as nature's architectures and solutions against pathogens;
- Mimicking the synthesis routes and processes of natural systems.

2. BIO-INSPIRED ANTIMICROBIAL NANOMATERIALS: COMPOSITION, DESIGN STRATEGIES AND EFFICACY

Close synergy among chemistry, biology and medicine allowed widespread application of nanomaterials in diagnosis, monitoring, treatment and therapy of many pathologies [15, 16].

The main advantages of nanostructures (NSs) with respect to larger sized particles are small dimensions, high surface-to-volume ratio and hence higher surface energy, and unique optical, electronic and magnetic properties [17-20]. Furthermore, they allow easy surface functionalization with biomolecules, thus opening novel opportunities for their use in drug delivery and biomedical field. However, these nanostructures could accumulate in the body, causing several risks for the health. Consequently, the perspective to prepare nanostructures with natural eco- and bio-friendly components represent the strategic way to reduce the toxicity [16, 21].

In this way, "bio-inspiration" has been currently permitting the design and formulation of novel friendly nanostructures with higher potentialities for biomedical applications. Almost all natural materials are composites of some form, comprising a relatively small number of polymeric, like proteins or polysaccharides, and ceramic components or building blocks, which are often composites themselves. From this limited toolbox, a wide range of hybrid materials and structures have been realized [21]. Recently, a great attention is focused on the design and formulation of bio-inspired antimicrobial nanostructures/nanoparticles with the aim to improve the efficacy as biocide agents [22, 23]. Actually, nanoparticles (NPs) are a promising solution to the major issue of antibiotic resistance [21]. Outstanding properties, such as their active surface area, chemical reactivity and biological activity, should allow them to closely interact with microbial surfaces, and thus elicit an antimicrobial effect that is not solely due to released components [24].

Nanoscale materials investigated for antimicrobial activity can be broadly grouped into three main categories, as overviewed in Fig. (**1**) [21]: -(1) inorganic particles such as noble metals (gold, silver, and platinum), magnetic (iron, cobalt, and nickel), and ceramic semiconductors (oxides of titanium, zinc, cadmium); -(2) organic which include carbon-based nanostructures; -(3) hybrid nanostructures which usually involve a combination of both organic and inorganic composition at the molecular level.

Nanostructures from each of these categories have been used as antimicrobial agents for a variety of specialized applications as detailed in relevant reviews [15, 25-31]. Most conventional physical and chemical processes of NP synthesis are associated with drawbacks. They usually involve high energy physical procedures as well as toxic and expensive chemicals, thus bringing high purification and production costs and limiting their application in the biomedical field. On the other hand, adopting a bio-inspired approach to NPs design can help to overcome these troubles as well as toxic-

ity issues. Actually, bioinspired approach provides sustainable and environmentally friendly procedures involving mild reaction conditions (*i.e.*, low temperature and pressure, and neutral or near-neutral pH). Furthermore, it offers high versatility for a wide range of compositions as well as selectivity. Moreover, synthesis conditions and employed biomolecules allow a fine control of composition and structure down to the molecular scale, thus affording fine tuning of materials properties, which cannot be achieved with conventional approaches. Finally, obtained materials would be endowed with intrinsic characteristic of biomolecules, including excellent biocompatibility, good aqueous stability as well as poor toxicity [32]. Therefore bio-inspired nanostructures have becoming more and more popular. In the following paragraphs, we are reviewing the most promising bio-inspired approaches to the development of antimicrobial nanostructures.

2.1. Bio-inspired Inorganic Nanostructures

Inorganic nanoparticles investigated as antimicrobial agents include both metals and ceramics.

Two approaches can be identified in the bio-inspired synthesis of these systems [32]:

- Functional biomimetic synthesis (FBS)
- Process biomimetic synthesis (PBS)

Functional biomimetic synthesis (FBS) aims at mimicking nature's strategies against pathogens, thus exploiting specific antimicrobial properties of natural materials/ structures/systems. Process biomimetic synthesis identifies a synthesis method, that attempts to prepare nanomaterials by mimicking the synthesis routes, processes, or procedures of natural substances and materials/structures [32].

2.1.1. Bio-inspired Metal Nanostructures

2.1.1.1. Bioinspired Synthesis Strategies

Metals have been used for centuries as antimicrobials. Among nanostructures, silver nanoparticles (AgNPs) are the most widely explored biocide agents due to their exceptional antibacterial properties and broad antimicrobial spectrum.

With high activity against a wide range of bacteria, Ag NPs have been widely used in water purification, food preservation, wound dressings and cosmetics, having low toxicity to human cells, high thermal stability and low volatility.

Besides silver nanoparticles, other metal nanomaterials have also been studied for antimicrobial treatment, including gold [33], copper [34-37], tellurium [38, 39], and bismuth [40].

Two strategies can be distinguished within bioinspired synthesis of metal nanoparticles:

- Surface modification with bio-macromolecules.
- Biogenic synthesis

The former can be classified as a functional biomimetic synthesis (FBS) approach, whereas the latter features as a process biomimetic synthesis.

Both allow a fine control of nanoparticles size as well as size distribution, as shown in Fig. (**2**), that reports TEM micrographs of some metal nanoparticles obtained using these approaches.

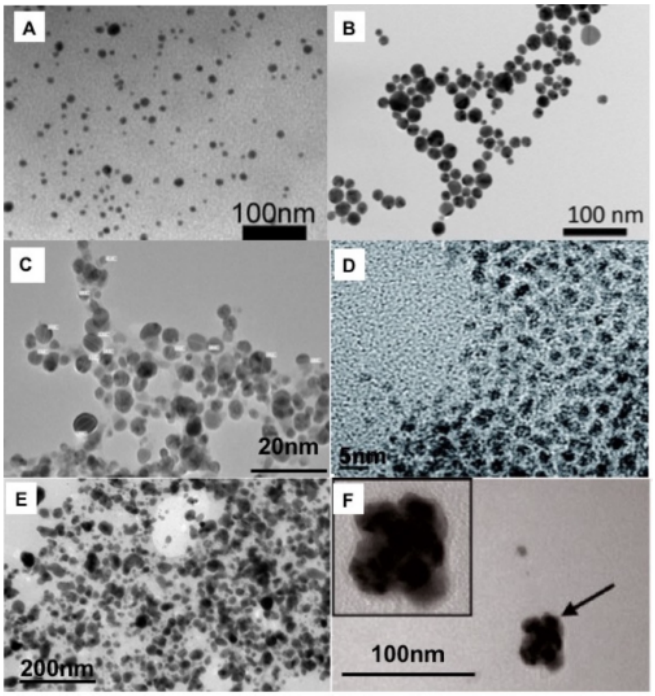

Fig. (2). TEM images of: (**A**) quercetin conjugated AgNPs, from Ref. [42]; (**B**) chitosan-Au nanostructures, from Ref. [46]; (**C**) AgNPs synthesized using *Artemisia annua* leaf extract, from Ref. [66]; (**D**) PtNPs by reduction with SF–SH from Ref. [71]; (**E**) AgNPs mediated by the biosurfactant extracted from corn steep liquor, from Ref. [53]; (**F**) Ag shell-Au nanocomposites synthesized using banana peel extract, from Ref [70].

Despite their intrinsic biocide activity, metal NPs are often further decorated with biomolecules, in order to combine potent antibacterial efficacy, environmental safety as well as low toxicity [41]. Wang et al conjugated [42] Ag NPs to 3,3′,4′,5,7-Pentahydroxyflavone (quercetin, Qe), a highly abundant flavonoid from fruits and vegetables (Fig. **2A**).

Bactericidal bio-polymers have also been coupled to metal nanoparticles to target wide range of bacteria [43,44]. In particular, chitosan, a deacetylated derivative of chitin, which is a natural polysaccharide present in the exoskeletons of crustaceans, insects, and certain fungi, is highly desirable for antimicrobial applications for its cheap, biocompatible and biocide features [45]. Several studies report chitosan conjugation to metal nanoparticles (Fig. **2B**), showing the dual role of chitosan as reducing and stabilizing agent thanks to the coordinative and reductive action of its amino groups [46].

Recently, surface functionalization of metal nanoparticles with antimicrobial peptides (AMPs) has been emerging as an effective bioinspired strategy to improve biocide performance of these systems. Antimicrobial peptides (AMPs), composed of 10–50 amino-acid residues, are an important component of the innate immune system [47], thus they appear as one of the most promising bio-inspired solutions to drug resistant pathogens [48]. However, bringing AMPs into clinics requires to improve their low stability, high toxicity and

Table 1. Summary of antimicrobial activity of metal nanoparticles synthesized from microbes and plants.

NP	Source	Antimicrobial Activity	Reference
Ag/Au	Liquid stream fermented by lactic acid bacteria	*Escherichia Coli*	[53]
Ag	Lysinibacillus varians	*Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Candida albicans*	[56]
Ag	Ochrobactrum anhtropi	*Salmonella typhi, Salmonella paratyphi, Vibrio cholera, Staphylococcus aureus*	[57]
Ag	Kluyveromyces marxianus Candida utilis 22	*Staphylococcuc aureus, Escherichia coli, Pseudomonas flourescence, Candida albicans, Candida glabrata, Candida krusei*	[58]
Ag	Kinneretia	*Candida albicans, Candida tropicalis, Bacillus cereus, Bacillus subtilis, Staphylococcus aureus, Salmonella enterica, Pseudomonas aeruginosa, Escherichia coli, and Vibrio parahaemolyticus*	[59]
Ag	Streptacidiphilus durhamensis	*Pseudomonas aeruginosa, Staphylococcus aureus, Proteus mirabilis, Escherichia coli, Klebsiella pneumoniae, Bacillus subtilis.*	[60]
Ag	Streptomyces narbonensis	Gram-positive (*Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli*) and yeast (*Candida albicans*)	[61]
Ag	Sargassum incisifolium	Gram-negative (*Acinetobacter baumannii, Klebsiella pneumoniae subsp. Pneumoniae*)	[62]
Ag	Fusarium oxysporum	Fungi *Aspergillus fumigatus*, *Alternaria alternata*, *Trichoderma parceramosum*, *Penicillium citrinum, Paecilomyces variotii*, *Candida albicans*, *Candida glabrata*, *Trichophyton mentagrophytes* and *Microsporum gypseum* Bacteria *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella typhi, Klebsiella pneumoniae*	[63]
Ag	*Aloe vera* leaf extract	Antifungal activity against Rhizopus sp. and Aspergillus sp.	[64]
Ag	*Abelmoschus esculentus* (L.) pulp extract	*Bacillus subtilis, Bacillus cereus, Escherichia coli, Micrococcus luteus, Pseudomonas aeruginosa*	[65]
Ag	Artemisia annua	Gram-negative (*Escherichia coli, Pseudomonas aeruginosa*), Gram positive (*Staphylococcus aureus, S Staphylococcus Epidermidis, Bacillus subtilis*)	[66]
Ag/Au	Indigofera tinctoria leaf extract	Bacteria and Fungi	[68]
Ag/Au	Red cabbage extract	Gram-positive (*Staphylococcus aureus*); Gram-negative (*Escherichia coli*); Fungi (*Candida Albicans)*	[69]
Cu	Zingiber officinale Extract	*Escherichia coli*	[72]
Ag	Olax scandens leaf extract	*Escherichia coli*	[73]

inefficient delivery to the target site at high concentrations [49]. Actually, peptide conjugation to nanoparticles is a valuable strategy to solve these problems and improve stability to aggregation of nanoparticles at the same time [50]. Nevertheless, there are not many papers on surface functionalization of metal nanoparticles with peptides [51, 52].

Indeed, most of the conventional protocols for NP synthesis involve hazardous chemicals (both as reactants and by-products) as well as extreme conditions (high temperature, radiation), which could have numerous harmful effects on the environment and human health. For this reason, these processes often require specialized apparatus and accurate purification before their use in clinical as well as food-packaging applications [53]. This issue prompted the development of new synthetic procedures that integrate the Process Biomimetic Synthesis (PBS) [54] with green chemistry approach. Actually, biological systems (plant and microorganisms) display a vast variety of biomolecules able to mediate reduction of metal salts to nanostructured elemental forms and stabilize nanostructures at the same time [53].

Biosynthesis of metal nanoparticles relies on clean, non-toxic and environmentally safe processes. Therefore, it can help to reduce environmental impact, minimize waste, improve energy efficiency in the field of nanomaterials. Furthermore, produced nanostructures show relevant biocide and biological properties. Therefore, this bioinspired approach looks an extremely valuable strategy to convert biowastes into high value biomedical products.

Elementary biomimetic synthesis via biomass template has been applied to produce antimicrobial metal nanoparticles, using biosurfactants by different sources: strains of bacteria [55-60], yeast [61, 62] or fungi [63], as well as plant extracts [64-73] or waste materials [74], as summarized in Table **1**.

Biosufactants play a key role in the reduction of the metal precursor, as well as in the stabilization of the resulting NPs.

Recently, Sardar *et al.* found that Artemisia annua leaf extract caused fast reduction of silver ions leading to the formation of silver nanoparticles in solution (Fig. **2C**) [66]. Similarly, Dhar *et al.* proved that thiol-modified silk fibroin (SF-SH) from *Bombyxmori silkworms* could act as a reducing agent, stabilizing agent, and material matrix in synthesis of noble metal NPs (Fig. **2D**) [71]. Moreover, a new, safe and promising bio-surfactant extracted from corn steep liquor was used for the biosynthesis of gold and silver nanoparticles (NPs) in a one-step procedure induced by temperature (Fig. **2E**) [53].

Biomass template approach can also be exploited to produce metal nanocomposites. In the study reported by Bankar *et al.*, bio-inspired Ag–Au nanocomposite was synthesized using banana peel extract (BPE) powder (Fig. **2F**) [70].

2.1.2. Antimicrobial Efficacy and Biological Properties

Antibacterial activity of silver nanoparticles, results from a combined effect of cell wall collapse, disruption of respiratory functions, and further damage towards proteins and DNA [75-77]. This combined mechanism prohibits microbes from mutating or developing antibiotic resistance to silver ions and AgNPs, which is a serious and growing concern for other chemical antimicrobial agents [78, 79]. Recent studies also suggest that Ag nanoparticles can generate reactive oxygen species (ROS), specifically superoxide radicals ($O_2^{\bullet-}$), which are toxic to bacterial cells [80].

Bioinspired metal nanoparticles usually combine poor cytotoxicity with higher antimicrobial performance than those obtained through conventional methods. Surface conjugation with bio-available moieties, such as quercetin produces an enhancement of the antibacterial effect against drug resistant *Escherichia coli* and *Staphylococcus aureus*.

Several studies prove that synergistic interaction between silver nanoparticles and antimicrobial peptides (AMPs) results in a marked increase of biocide efficacy with respect to bare components [81-83]. In particular, Zheng *et al.* found that silver nanoclusters conjugated with daptomycin, displayed improved bacterial killing efficiency compared to the physical mix of daptomycin and silver nanoclusters [83]. Similarly, Lambadi *et al.* have recently presented silver nanoparticles modified with polymyxin B with improved antibacterial potential against MDR clinical *Vibrio fluvialis* and nosocomial *Pseudomons aeruginosa* when compared to bare AgNPs [84]. Furthermore, Mohanty *et al.* proved that silver nanoparticles obtained from bacterial, fungal and plant biomasses, combined with the NK-2 (KILRGVCKKI MRTFLRRISKDILTGKK-NH_2) and LLKKK-18 (KEFKRIVKRIKKFLRKL), are endowed with potent antimicrobial activity against mycobacteria [85].

Biogenic derived metal nanoparticles are usually endowed with high biocompatibility and significant antibacterial towards both Gram-positive and Gram-negative strains [66]. In particular, AgNPs, synthesized from a Fusariumoxysporum fungal filtrate (FF) solution, showed strong antimicrobial activity against Candida parapsilosis and Xanthomonas axonopodis pv. Citri. [63]. Indeed, some of the biosurfactants proposed in the literature are produced by pathogenic microorganisms, thus reducing their applicability in the synthesis of NPs for biomedical applications [53]. However, a huge number of safe biosurfactants are also available, such as extracts from corn liquor (BS), that proved to be useful to obtain biocompatible BS-Ag NPs with high antimicrobial activity, against gram-negative bacteria like *Escherichia coli*, at a very low silver concentration [53]. An outstanding property of biogenic nanoparticles is their activity against biofilm producing bacteria. Ag–Au nanocomposite synthesized using banana peel extract (BPE) powder exhibited enhanced antimicrobial activity against *Pseudomonas aeruginosa* and highest biofilm inibition (70–80%) when compared with individual AgNPs and AuNPs, as shown by the marked signal decay in fluorescence images (Fig. **3**) [70].

As a major point, bio-inspired metal nanoparticles can show multifunctional behavior [65,73,74]. Several studies report that chitosan conjugation to metal nanoparticles not only improves and prolong their antimicrobial effectiveness against both Gram-positive and Gram-negative strains (Fig. **3**) [46, 86-91], but also enhances anti-inflammatory and wound healing effect [87, 92]. In particular, Yao *et al.* proved that chitosan conjugated silver nanoparticles were effective against methicillin-resistant *Staphylococcus aureus* (MRSA) (Fig. **4A**) and promoted faster topical wound healing rate (Fig. **4B**) in a in a dorsal MRSA wound infection mouse model.

In the field of metal nanoparticles conjugated to antimicrobial peptides, Chen *et al.* [93] prepared gold nanodots (AuNDs) via that co-deposition of both surfactin and 1-dodecanethiol as sketched in Fig. (**5A**). SFT-conjugated AuNDs displayed higher stability to aggregation, membrane lysis behavior (Fig. **5A**) and more pronounced antimicrobial activity, also against multidrug-resistant bacteria, with minimal inhibitory concentration much lower than surfactin alone (Fig. **5B**). These properties were also combined with faster wound healing action and better epithelialization in the treatment of methicillin-resistant *S. aureus*–infections (Fig. **5C**) [50, 93].

Similarly, studies of Ferreira *et al.* showed that (AMP)LL37- Au NPs, whose preparation is sketched in Fig. (**6A**), combined antimicrobial with pro-regenerative properties. More in detail, keratinocyte migration assay (on human HaCaT cell line and human primary keratinocytes, Fig. (**B-D**) and skin wound healing assay proved LL37-Au NPs higher *in-vitro* and *in-vivo* bioactivity than soluble LL37 peptide [94].

From these studies, it is therefore clear, that AMP-conjugated NPs may offer great opportunity to improve stability and antimicrobial effects, while reducing toxicity [49,50]. However, some studies show that metal nanoparticle/peptide conjugates may have cytotoxic effects also on eukaryotic cells, when triggered by light/NIR; therefore, this aspect needs to be further evaluated [95, 96].

Finally, bio-surfactants employed in biogenic synthesis act not simply as templates, but as functional modifiers, that confer to the final nanostructures peculiar biological properties. Recently, silver nanoparticles (b-AgNPs) produced by Chowdhury *et al.* [73] using Olax scandens leaf extract were endowed with multiple biological properties, as summarized

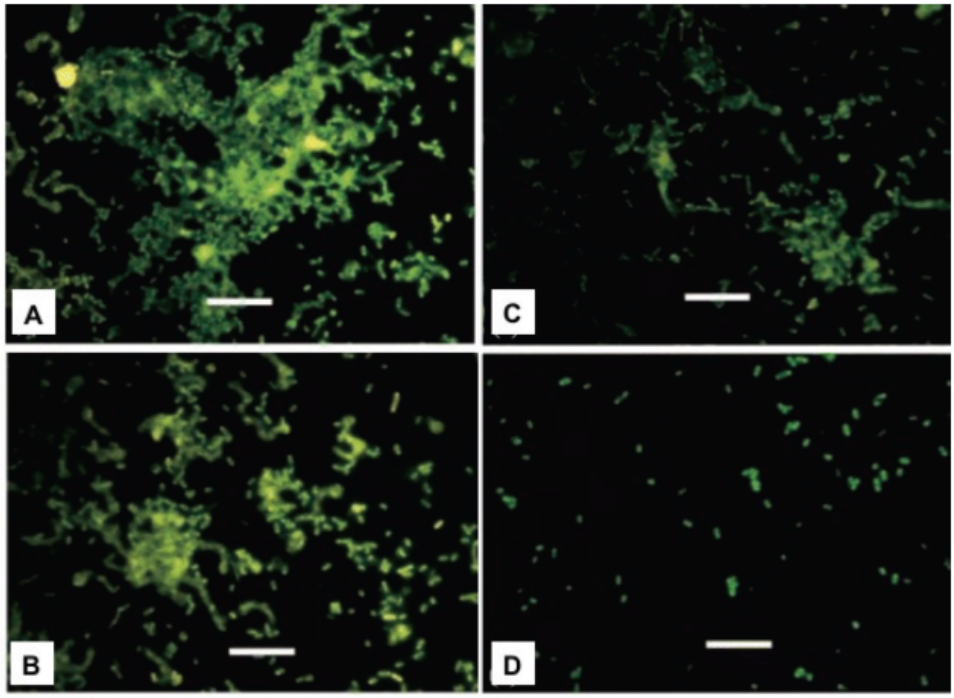

Fig. (3). Fluorescence images of (**A**) biofilm formation by P. aeroginosa without NPs (control) and in the presence of (**B**) AgNPs, (**C**) AuNPs and (**D**) Ag–Au nanocomposite. (Inset bar: 10 μm). From Ref. [70].

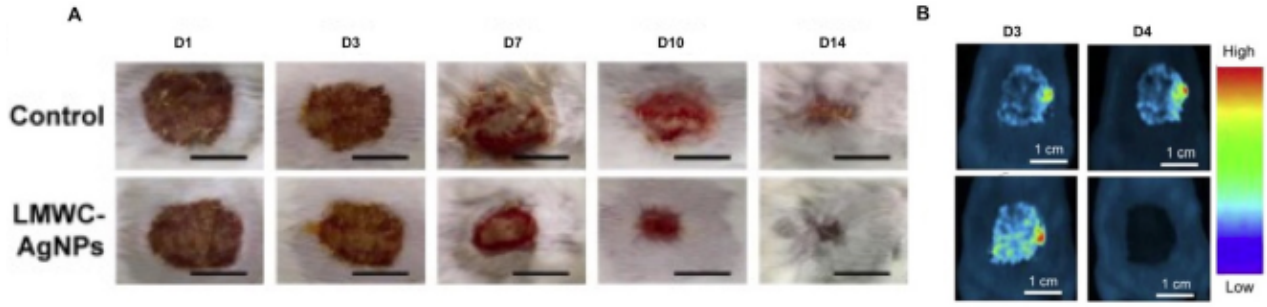

Fig. (4). (**A**) Fx CC D luminescent camera images of wound infection and healing. (Scale bar: 1 cm); (**B**) Fx CC D chemiluminescence assay on mice wounds inoculated with methicillin-resistant Staphylococcus aureus (MRSA) dressed with LMWC-AgNPs. Higher intensity of the red color indicates more severe infection. From Ref. [87].

in Fig. (**7**). They showed biocompatibility, enhanced antibacterial activity and even anti-cancer efficacy against different cancer cells (A549: human lung cancer cell lines, B16: mouse melanoma cell line & MCF7: human breast cancer cells) (anti-cancer). Furthermore, provided bright red fluorescence inside the cells due to ROS productions (Fig. **7**), thus allowing cancer cells staining and localization by fluorescence imaging.

2.1.3. Bioinspired Ceramic Nanoparticles

A great many studies proved the antibacterial activity of metal oxide nanomaterials, such as zinc oxide (ZnO), copper oxide (CuO) [97, 98], magnesium oxide (MgO), titanium dioxide (TiO_2) [99], aluminum oxide (Al_2O_3) [100], magnetic iron oxide (α-Fe_2O_3) [101], and cerium oxide (CeO_2) [102] nanoparticles [29]. Furthermore, inorganic metal oxide nanomaterials have been attracting great attention as potential delivery systems for antimicrobial peptides (AMP) [103]. Actually, inorganic nanomaterials provide increased stability from chemical and enzymatic degradation, reduced aggregation and/or conformational changes, controlled drug release rate, increased bioavailability and reduced toxicity [47, 103]. An encouraging example of antibacterial magnetic nanoparticles combined with cationic antimicrobial peptides has been recently reported [104]. In particular synergistic or additive effects were observed when core–shell MNPs were conjugated toceragenins (CAP)]. Although silica is not endowed with intrinsic antimicrobial activity, it has attracted considerable attention as delivery system of antimicrobial peptides, for its biocompatibility, tunable size and porosity as well as functional versatility [105]. Non-porous silica particles build up a stable LL-37 surface coating due to their higher negative surface charge, and display large membrane interactions and antimicrobial effects [106]. In the continuous look for biomimetic antimicrobial products shrimp shells were exploited as a novel and green source of precursors to produce calcium oxide nano-plates, which showed effective antimicrobial activity against both gram positive and

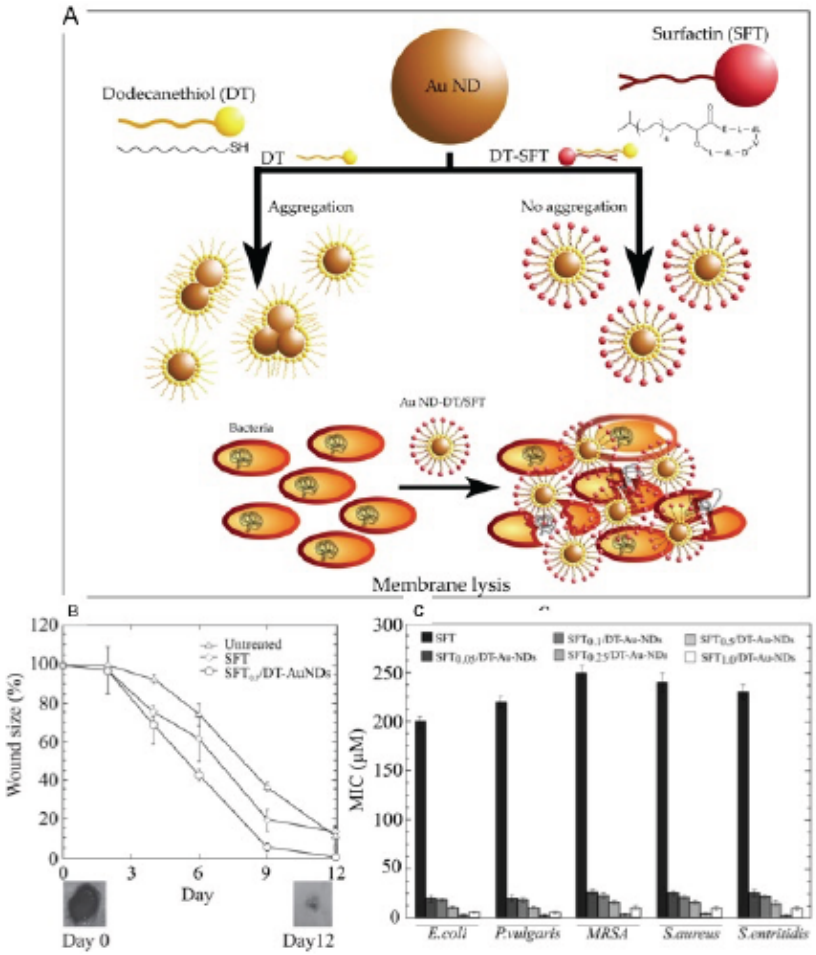

Fig. (5). (**A**) Scheme of the synthesis of surfactin-modified gold nanodots (AuNDs). Surfactin allows to obtain AuNDs able to disrupt bacterial membranes; (**B**) Healing ofMRSA-infected wounds, expressed as wound area relative to the initial area, for rats either untreated or treated with free surfactin or surfactin-modified AuNDs; (**C**) Minimum inhibitory concentrations (MICs) for surfactin in solution (SFT) and after complexation with AuNDs (SFT/DT-AuNDs) at the indicated ratios. From Ref. [50]

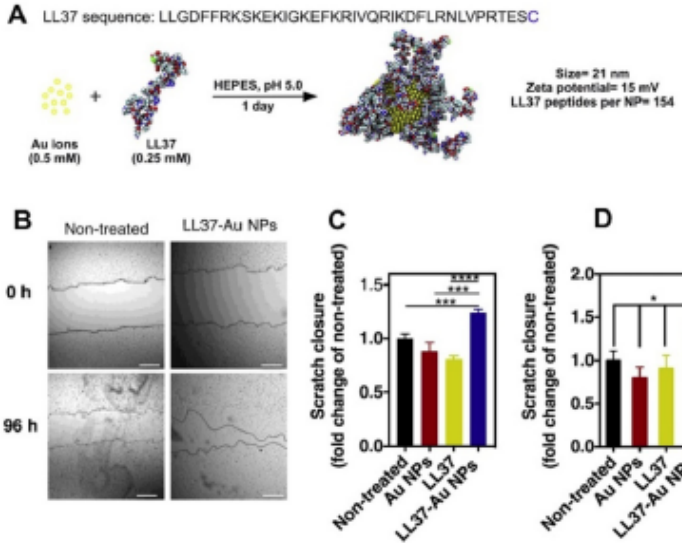

Fig. (6). (**A**) Schematic representation of Au NP synthesis in the presence of LL37 peptide; (**B**) Scratch assay of keratinocytes (HaCaT cells) after 96 h of incubation without and with LL37-Au NPs (15 μg/mL): (**C**) Light microscopy images of the healing of the scratch at 96 h (HaCaT cells, Scale bars: 1 mm). (c.2) Quantification of scratch closure at 96 h (**D**) Scratch closure in human primary keratinocytes at 24 h. *P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001 indicate statistical significance between treatment groups. From Ref. [94].

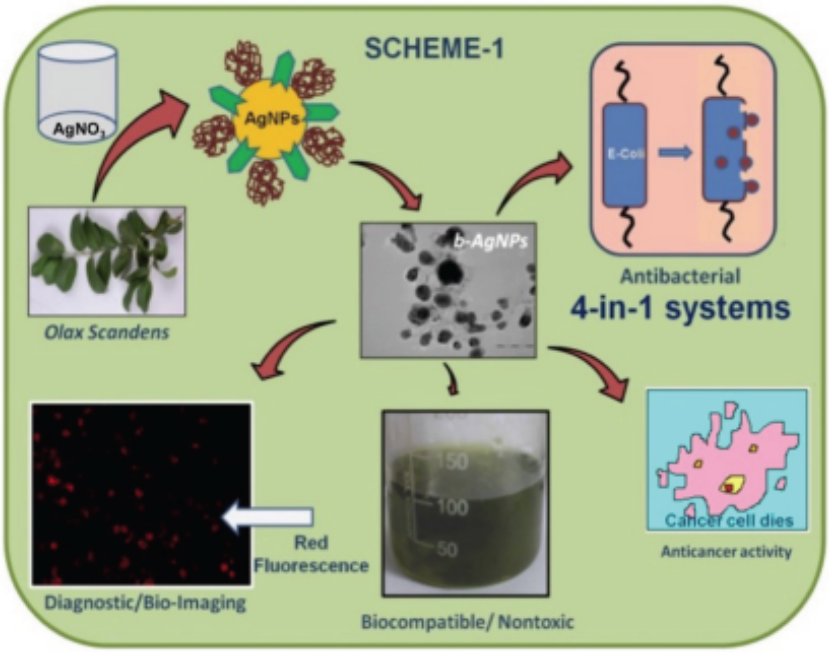

Fig. (7). Scheme of the synthesis, characterization and biomedical (diagnostic, anticancer and antibacterial) applications of biosynthesized silver nanoparticles (b-AgNPs) using Olax Scandens leaf extract. From Ref. [73].

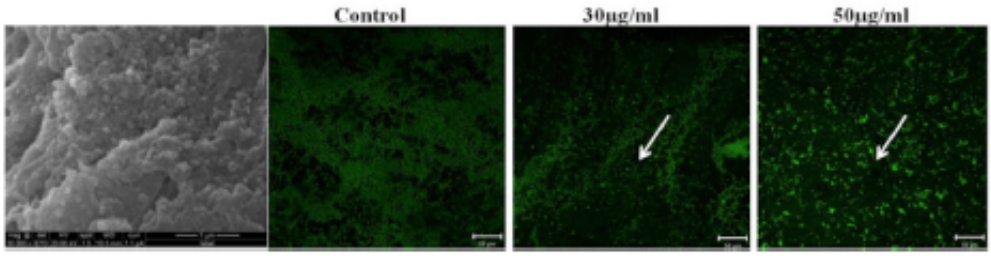

Fig. (8). SEM and Confocal laser scanning microscopy images of *C. albicans* biofilms on CS/Ag/ZnO nanocomposite. From Ref. [110].

gram-negative bacteria [107]. Moreover, as for metal nanoparticles, several metallic oxides, and metal-salt NPs have been obtained by process biomimetic synthesis, mimicking biomineralization processes. Specifically, long-chain polyamines involved in some biomineralization processes, were employed to nucleate, organize, and deposit nanostructured ZnO on cotton fabric in an aqueous solution under mild conditions (room temperature and neutral pH). Obtained ZnO particles showed efficient antibacterial activity against both Gram-positive and Gram-negative bacteria [108]. Similarly, in polyamine-mediated ZnO mineralization, polyamine also acted as a reducing agent of Ag^+ ions. Obtained Ag/ZnO nanostructures, exhibit efficient antimicrobial activity against both Gram-positive and Gram-negative bacteria [109]. Within process biomimetic synthesis, polysaccharide-mediated biomineralization where minerals are salts of essential metallic ions like Zn(II), represents a promising strategy for designing multifunctional biomaterials for potential biomedical applications [110]. New bioactive and antimicrobial biomaterials were produced by alginate-mediated biomineralization with Zn-mineral phase. The obtained nanocomposites exhibit strong antimicrobial effect against *Escherichia coli, Staphylococcus aureus* and *Candida albicans* [111]. In a recent study, Vaseeharan *et al.* synthetized chitosan coated Ag/ZnO (CS/Ag/ZnO) nanocomposite, with high antifungal and antibacterial activity against both Gram positive (*B. licheniformis* and *B. cereus*) and Gram negative (*Vibrio parahaemolyticus* and *Proteus vulgaris*) bacteria [110] (Fig. **8**).

In another study, hierarchically structured cellulose@ZnO composites (Fig. **9A**) have been synthesized by an environmentally friendly hydrothermal and solvothermal methods [112, 113]. Hierarchical structure resulted in an enhancement of antimicrobial activity against the Gram-positive bacterium *Staphylococcus aureus* and the Gram-negative bacterium *Escherichia coli* [112] (Fig. **9B**).

Bacteria adhesion to mineral surfaces is a widespread phenomenon. Recent studies have shed light onto its molecular-scale mechanisms, showing that strong interfacial interactions are established between bacteria and clay minerals, through the extracellular polymeric substances (EPS), a mixture polysaccharides, proteins, nucleic acids, and lipids, secreted by microorganism during their growth. These interactions play an important role in phenomena such as biofilm formation, bacterial cell adhesion and migration as well as biomineralization. This intriguing natural adsorption phenomenon inspired the design of biomimetic antimicrobial clays with bacterial cell-specific adhesive and membrane properties for *Helicobacter pylori treatment* [114]. These

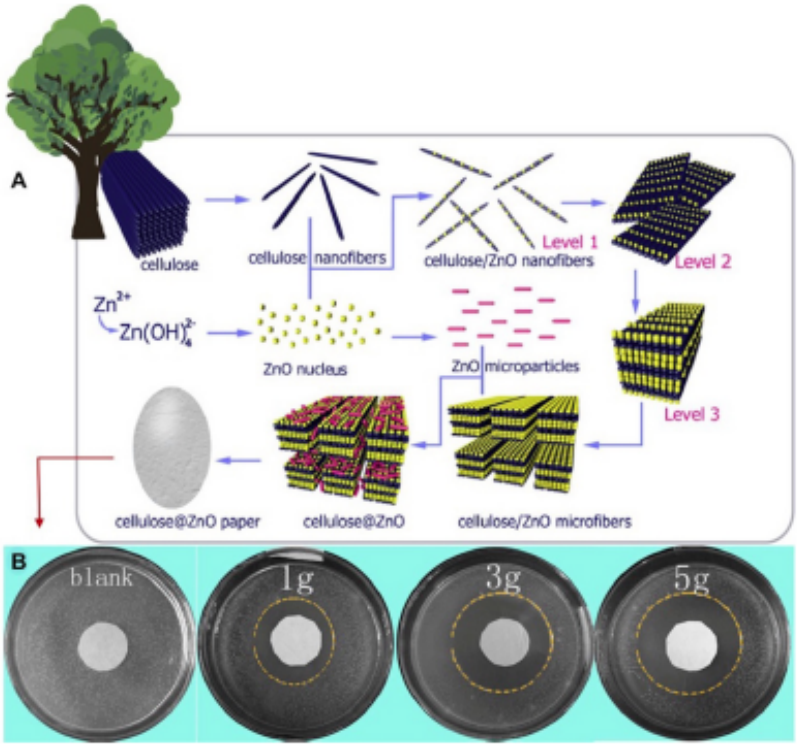

Fig. (9). (**A**) Schematic model illustrating the formation of the cellulose@ZnO composite and (**B**) the Inhibition zones against *Staphylococcus aureus* and *Escherichia coli* of these composites prepared with different amounts of zinc acetate. From Ref. [112].

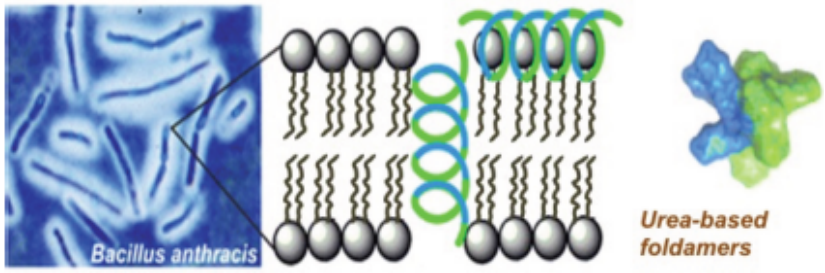

Fig. (10). Schematic illustration of the action mechanism of urea-based foldamers against bacterial cell membranes. From Ref. [117].

nanoparticles were self-assembled from highly exfoliated montmorillonite (eMMT) and cationic linear polyethyleneimine (lPEI) via electrostatic interactions. eMMT acts as a bio-inspired "sticky" building block for anchoring antibacterial nanoparticles onto the bacterial cell surface via bacteria-secreted extracellular polymeric substances (EPS), whereas lPEI is able to efficiently lyse the bacterial outer membrane.

2.2. Bio-inspired Organic Nanostructures

Organic features are also attracting the interest to realize bio-inspired nanostructures with antimicrobial properties. The most common organic molecules, such as peptides/proteins [115, 116] polymers/biopolymers and polysaccharides, represent good sources to realize nanostructures with biocidal activity. Indeed, the synthesis of bio-inspired unnatural backbones leading to foldamers was proposed to provide effective structural mimics of membrane active antimicrobial peptides (AMPs) with high properties in a physiological environment [117] (Fig. **10**).

As introduced in the previous paragraphs, these peptides are a unique and diverse group of molecules produced by a variety of plant, invertebrate and higher animal species, usually presenting amphipathic character and several charged residues [118]. By inspiring to these moieties, similar structural features were successfully reproduced in biodegradable antimicrobial nanostructures, capable to disrupt the bacterial membrane bilayer. Also, synthetic polypeptides, inspired by amino acid backbones found in nature, provided a powerful route to obtain biocompatible polymeric systems with highly antimicrobial function [119]. Recently, bio-inspired lipopeptide scaffolds with high antibiotic activity and low *in vivo* toxicity were designed as new chemicals with high activity and selectivity against multi-drug-resistant pathogens [8].

Moreover, bio-inspired peptides were also adopted to decorate dendrimers for a robust antibacterial coating on hydroxyapatite (HA), in order to resolve the problem of bacterial colonization on implanted biomaterials. [120] (Fig. **11**).

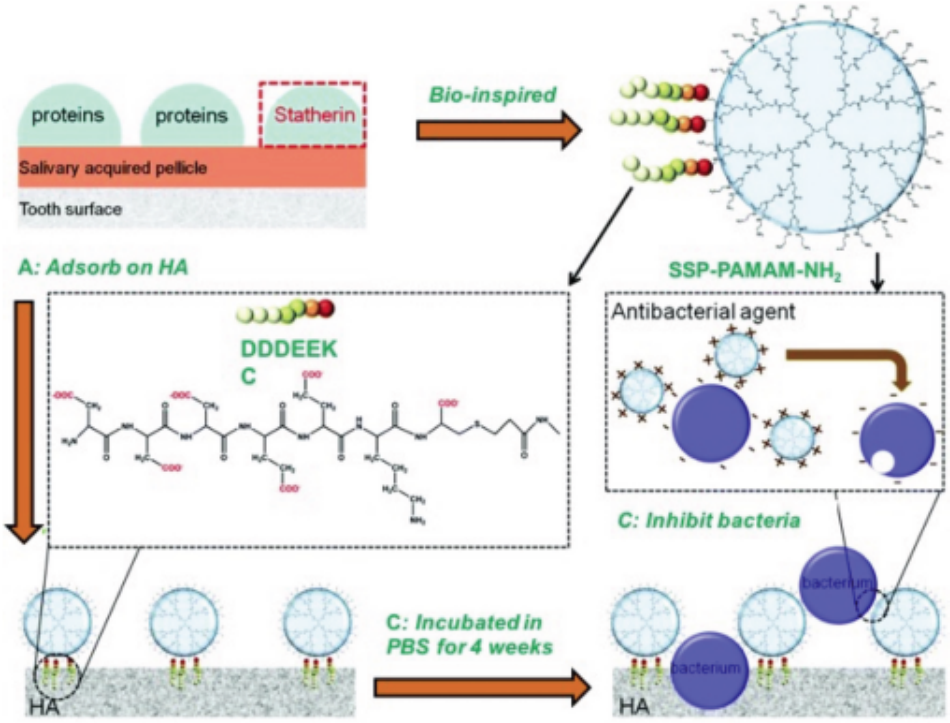

Fig. (11). Schematic demonstration of the specific adsorption of SSP-PAMAM-NH_2 on the HA surface and the subsequent long-term antibacterial activity. From Ref. [120].

Fig. (**11**) shows the design and mechanism of action of HA-anchored SSP-PAMAM-NH_2 dendrimer bioinspired from salivary statherin protein (SSP). Mimicking statherin, DDDEEK peptide has a binding capacity on HA surface, thus ensuring SSP-PAMAM-NH_2 adhesion onto HA surface. Furthermore, positive charge of amino groups inhibits bacterial adhesion on the surface.

Instead, self-assembly of DNA-porphyrin hybrid molecules were designed as efficient antimicrobial nano-networks against *Escherichia coli BL-21* Gram-negative and *Staphylococcus aureus* Gram-positive bacteria. Interestingly, these DNA-porphyrin nano-networks afforded highly efficient and coherent photo-induced reactive oxygen species (ROS) generation to display antimicrobial activity [121].

Although natural peptides still represent a valid choice to produce safe antimicrobial nanomaterials with high efficacy [48, 53], the scientific interest was also strongly focused on the possibility to replicate these macromolecular structures by synthetic routes [122]. Indeed, by studying these peptides to identify key aspects of structure and composition, suitable synthetic polymer mimics were designed as potential anti-infective agents. In particular, amphiphilic antimicrobial polymers showed potential antimicrobial properties and low susceptibility for developing resistance, unlike small molecular antibiotics [123]. The design of various types of macromolecular architectures with control of structural parameters, such as hydrophobicity/ hydrophilicity balance, molecular weight, and ionic groups, is strikingly related to the antimicrobial activity, inducing the design of advanced polymeric assemblies with well-defined nanostructures. Specifically, guanidine based poly(methylmethacrylate-co-2-guanidinoethyl methacrylate) (pMMA-co-GEMA) copolymers with low molecular weight and low methyl content also revealed good potentiality by *in vitro* testing against monomicrobial and polymicrobial biofilms of the *Staphylococcus aureus* bacteria and the *Candida albicans fungus*[124].

At the same time, a combination of peptides and polymers with antimicrobial properties is positively considered: peptide-grafted hyperbranched polymer nanosheets with weak positive charges were recently synthesized, showing excellent intrinsically antibacterial efficacy against typical Gram-positive and Gram-negative bacteria by acting through a "wrapping and penetrating" antibacterial mechanism (Fig. **12**) [125].

However, due to reduction of non-renewable sources and strong marketing sustainable strategy in the last decade, an increasing attention was focused on attractive environmentally friendly solutions to develop novel biomaterials. Biopolymers and polysaccharides are a group of molecules with special benefits with respect to the synthetic polymers because they are nontoxic, biodegradable, recyclable and obtained from renewable resources. Polydopamine (PDA) is a biomimetic polymer that is based on the mussel adhesive protein excreted by many marine organisms and produced by self-polymerization of dopamine under oxidative and alkaline conditions, similar to those of seawater [126]. PDA has been used extensively in many other applications because of its adhesive and cohesive properties [126], which are believed to be related to the reactivity of poly(o-quinone-indole) backbone to form covalent bonds with various substances. Moreover, the catecholic moiety of PDA can be

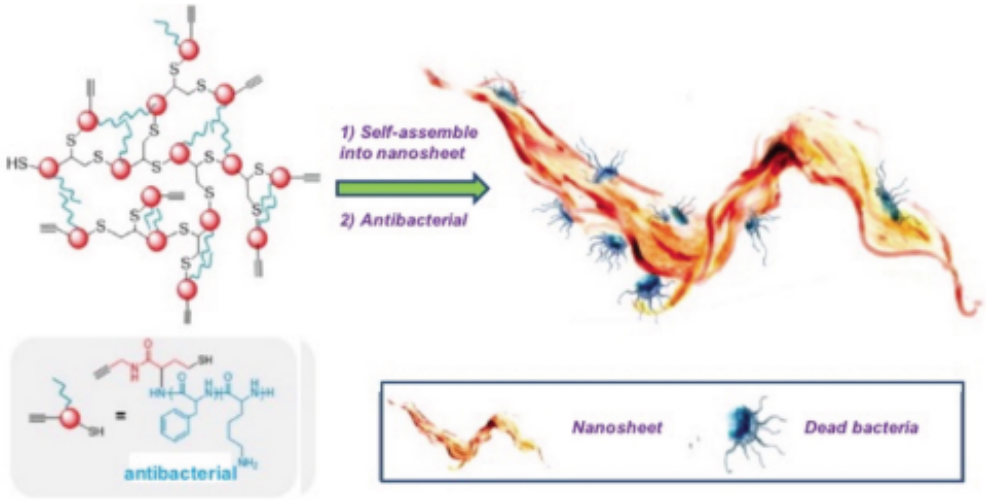

Fig. (12). Schematic Illustration of the formation of intrinsically antibacterial nanosheets by peptide-grafted hyperbranched polymer and subsequent "wrapping and penetrating" antibacterial mechanism. From Ref. [125].

involved in hydrogen bonding, metal complexation, π−π interactions. Nanostructures of polydopamine, a dark brown-black insoluble biopolymer produced by autoxidation of dopamine, have shown a high biocide activity [24], proposing as valid alternative to synthetic polymers. Analogously, the linear polysaccharide chitosan, obtained by deacetylation of chitin which constitutes the outer skeleton of insects and crustaceans, was also used to produce antimicrobial bio-inspired hydrogels [127] and films with high antimicrobial activity against *Escherichia coli* and *Staphylococus aureus* [128].

2.3. Bio-inspired Hybrid Nanostructures

As widely described in the previous paragraphs, a huge variety of inorganic and organic antimicrobial nanostructures were realized following a "bio-inspired" approach. More recently, a great attention has been focused on the design and synthesis of hybrid inorganic/organic nanostructures, presenting novel properties not simply deriving by a combination of the single components. In this context, novel bio-inspired antimicrobial hybrid nanostructures were proposed by conjugating/blendingin the molecular scale, during synthesis step, either metals or inorganic components with peptides, biopolymers or other organic molecules. Among metal oxide nanoparticles TiO_2-NPs are known to be cost effective, stable and safe for humans and the environment. A unique property of TiO_2-NPs is the photocatalytic property resulting in enhanced microbicide activity on exposure to UV-light [129]. In the continuous look for novel bioinspired systems with enhanced antimicrobial activity, some researchers focused on eumelanins [130], negatively charged, high molecular weight, hydrophobic pigments widely dispersed in mammalians, plants and microorganisms [131, 132]. Many studies have recently shown that melanins interfere with numerous host defense mechanisms: they are highly immunogenic and have anti-inflammatory properties, protecting organisms against UV-radiation [133, 134], as well as microbial lysis. Indeed, melanization of skin and other tissues is an important component of the innate immune defense system: in this, the function of eumelanin in skin seems to inhibit the proliferation of bacterial, fungal and other parasitic infections of the dermis and epidermis. Several compounds have been explored to promote/catalyze oxidative polymerization of melanogenic precursors, such as 5,6-dihydroxyindole-2-carboxylic acid (DHICA), to melanin-like biopolymers *in vitro*. Eco-friendly hybrid Eumelanin-TiO_2nanostructures have been recently obtained through in situ methodology based on hydrothermal route [130, 135]. TiO_2 has shown photocatalytic activity driving DHICA polymerization and acting as a templating agent for eumelanin formation itself. This synthesis approach to hybrid TiO_2/melanin nanostructures, was based on the ability of DHICA to adsorb onto TiO_2 and act as a ligand for Ti^{4+} ions, through its catechol group, thus forming a ligand to metal charge transfer complex (LMCTC), that activates TiO_2 catalytic activity under visible light [130, 136]. The resulting melanin−TiO_2 hybrid nanostructures show higher antimicrobial activity than bare melanin towards Gram-negative *Escherichia coli DH5α* strain under UV irradiation and even visible light [130,136] (Fig. **13**).

Actually, the aggregation of nanoparticles has been shown to significantly reduce the activity of nanomaterials, resulting in inferior performance. As an alternative to the use of traditional stabilization of unstable nanoparticles (PEGylation, surface functionalization with synthetic surfactants), different bioinspired strategies to produce hybrid antimicrobial nanostructures have been proposed.

As discussed in Section 2.1 Silver nanoparticles (AgNPs) have been extensively used for their antibacterial activity. The unique chemical properties of polydopammine (PDA) have also inspired researchers to explore its application in the construction of micro- and nanocapsules to introduce new functionalities, including antibacterial activity [15, 138, 139]. Recently, a facile and one-pot oil−water sonochemical method was proposed for the synthesis of hybrid Cu/Ag-PDA-NPs. In this study, the oxidative conditions established during the sonication process are exploited to polymerize dopamine into PDA-NPs that can chelate metal producing highly biocide material. The combination of both metals in Cu/Ag-PDA-NPs is especially effective against bacteria and robust biofilms, owing to the dual bactericidal mechanisms

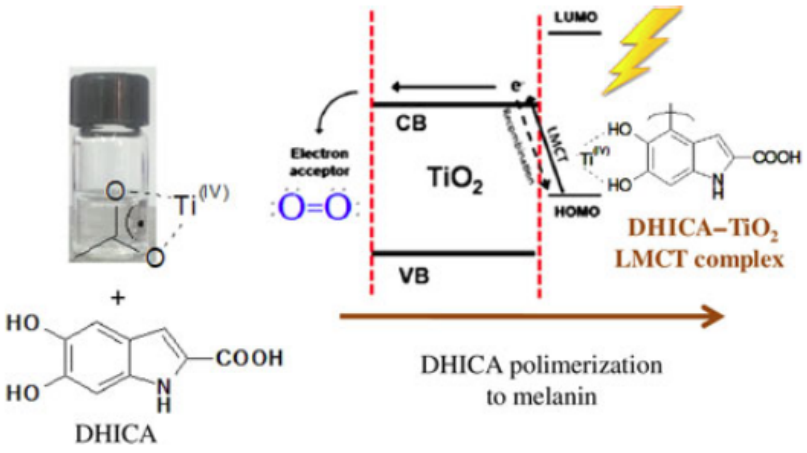

Fig. (13). Photocatalytic activity of TiO_2 for 5,6-dihydroxyindole-2-carboxylic acid (DHICA) polymerization and formation of melanin–TiO_2 hybrid nanostructures with biocide behavior. From Ref. [136].

of the metals. Furthermore, stable PDA-semiquinone and reactive oxygen species generated under physiological conditions, contribute at least partly to the antimicrobial activity which was preserved even after prolonged storage under ambient conditions [140]. An alternative bioinspired strategy to disperse and stabilize AgNPs in aqueous solution is the use of water-dispersible and biocompatible component such as a cellulose nanocrystal (CNC) [141]. CNC is produced from biomass via hydrolysis in strong acids. Biodegradable and biocompatible rod-shaped CNCs have attracted growing attention due to their extraordinary mechanical properties, high aspect ratio and surface area, colloidal stability, biocompatible sugar-based chemical structure, and cheap processing for a well-defined nanomaterial [142-144]. Actually, to combine nanoparticles with CNC, the adhesive characteristic of CNC surface must be improved. A facile and effective approach is to use dopamine to introduce a versatile chemical coating, yielding a surface with strong adsorption for most metallic nanoparticles. The resultant PDA phase also possesses excellent reduction and chelation properties towards metal ions [145]. CNCs were first modified with dopamine, followed by in situ generation and anchoring of AgNPs on the surface of CNCs through the reduction of silver ions by polydopamine coated CNCs. Comparing with free AgNPs, obtained hybrids nanosystem shows high dispersion stability in aqueous media enhanced by the CNC, which in turn results in more than fourfold increase in antibacterial activity against both Gram-positive and Gram-negative bacteria (Fig. **14A**) [141]. Ag NPs were also distributed on the surface of Fe_3O_4 nanoparticles using polydopamine as the intermediate layer (Fig. **14B**) [146]. In this study, silanization and thiol chemistry were used to firmly combine the Fe_3O_4-PDA core and outer surface Ag NPs producing hybrid spherical nanoparticles. The antibacterial activity of the Fe_3O_4-PDA-Ag was demonstrated against Gram-negative *Escherichia coli* bacteria. These systems can be applied as active nanomaterials for surface coating on the outer surface of hull to prevent the corrosion of hull from marine bacteria.

Photo-antimicrobials, antimicrobial drugs that are activated by light, are an emerging type of drugs that are currently being actively investigated to address the growing threat of antibiotic resistance [147]. Molecular and nanostructured materials based on organic dyes such as porphyrins and phthalocyanines (Pc) are widely used in materials science and nanotechnology [148, 149]. The field of Pc-based biohybrid materials is at a very early stage of research, but a number of biological nanostructures have been utilized, including peptides, antibodies, protein cages, DNA, liposomes and carbohydrates [150]. Key properties of Pc include high stability and absorption coefficients at the near-infrared spectral window, long-lived fluorescence, a rich electrochemistry, and high quantum yields of photo-induced singlet oxygen ($^1O_2$) generation (F_D) [151, 152]. Such properties are key features of photo-antimicrobials. Unfortunately, Pc tend to self-aggregate, especially in aqueous conditions, in which H-type stacks are normally formed [153]. This kind of aggregation leads to self-quenching of the excited state, limiting the applicability of these macrocycles. A growing strategy to circumvent such limitations involves creating bioinspired hybrid materials in which the optical properties of the chromophore are maintained or even enhanced. An easy, non-covalent approach has been proposed for the immobilization of cationic zinc Pc (ZnPc) derivatives on the sulfated surface of pristine cellulose nanocrystals (CNC) resulting in well-defined nanostructured Pc systems [154]. The Pc photodynamic properties, normally hindered in aqueous media due to aggregation, are preserved in the resulting complexes, leading to efficiently capacity to kill Gram-positive and Gram-negative bacteria, as well as pathogenic yeasts (Fig. **14C**). A good alternative to the creation of new materials for antibacterial applications, is to mimic existing and efficient biological systems. For instance, animals closely regulate iron levels [153] and sequester this nutrient as a mechanism of preventing bacterial proliferation. Two kinds of proteins play a key role in this process: transferrins (including lactoferrin), which are glycoproteins that remove extracellular Fe(III) due to their high Fe(III) affinity [155, 156] and ferritin, which stores the iron that is not required for immediate metabolic purposes [157-159]. Lactoferrin is considered to be one of the key components of the immune system, partly due to its high affinity for Fe(III), whereas ferritin consists of a spherical protein shell (apoferritin) surrounding an aqueous cavity that incorporates toxic Fe(II), which is oxidized during its journey to the cavity to form a Fe(III) mineral core therein.

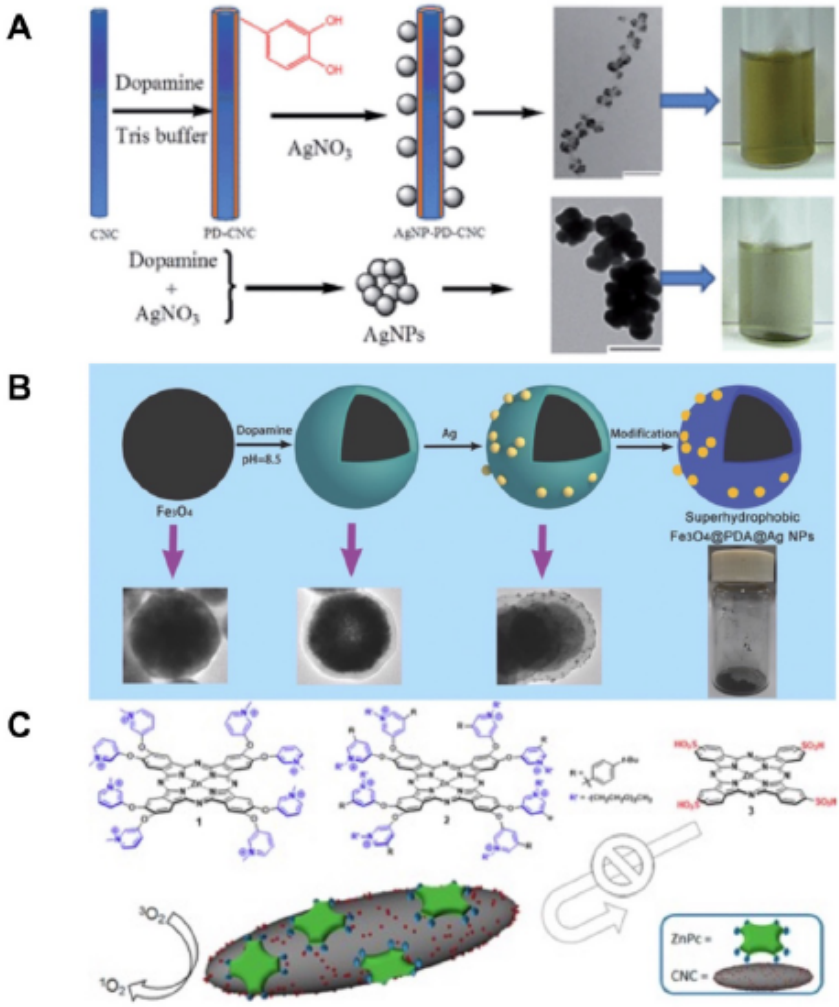

Fig. (14). (**A**) Preparation of PDA functionalized CNCs and silver nanoparticle immobilized CNCs. From Ref [141]; (**B**) Schematic illustration of synthesis procedures for Fe_3O_4@PDA@Ag NPs and corresponding TEM images. From Ref. [146]; (**C**) Chemical structure of the cationic ZnPc derivatives 1 and 2, and the anionic ZnPc 3 (top). Schematic representation of ZnPc immobilized supramolecularly onto the surface of sulfate-decorated CNC, as an example of nanostructured biohybrid (bottom). From Ref. [154].

The apoferritin shell is assembled from 24 polypeptide chains of two types, namely heavy (H) and light (L) subunits. It has traditionally been thought that H-subunits play a key role in Fe(II) oxidation as they contain catalytic ferroxidase centers, whereas L-subunits are associated with Fe(III) nucleation. It seems that the iron uptake and storage process requires the oxidative activity of at least a small number of H subunits. Nevertheless, pure or H-rich ferritin is frequently found in humans, especially in breast milk, the heart or serum, probably due to its strong ferroxidase activity, which helps to protect against toxic Fe(II) [160]. In light of these findings, a vinyl sulfone silica functionalized with both proteins in a step-by-step manner has been proposed. The resulting hybrid silica–protein material spatially confines both proteins and mimics breast milk to some extent. A high antibacterial activity has been demonstrated against *E. coli K-12* and the correlation between bacterial inhibition and iron uptake confirms that the antimicrobial activity of these materials resides in their iron uptake capacity [161].

Recent decades have witnessed rapid advancements in catalytic nanomaterial, creating a rather dynamic research field called "nanozymes": artificial enzymes designed to mimic natural ones in a great many aspects. In contrast to natural enzymes, nanozymes are easily produced in the laboratory or on an industrial scale, insensitive to external environment, tunable in catalytic activity with activators or inhibitors, and reusable, thereby exhibiting great promise in biosensing and biomedicine [162]. The antimicrobial properties of naturally occurring peroxidase systems are well-known. Human exocrine secretions such as milk, saliva, tears, seminal, vaginal, and gastrointestinal fluids, as well as human phagocytic cells, such as neutrophils, monocytes and eosinophils, contain peroxidase enzymes, which comprise part of the innate host defense system. Indeed, Peroxidases alone have no antibacterial effect. However, peroxidase exerts an antimicrobial effect indirectly by catalyzing the transformation of a substrate with low antimicrobial properties into one with high antimicrobial effects. The complete antimicrobial peroxidase system requires three components: a particular peroxidase enzyme, hydrogen peroxide (H_2O_2) and an oxidizable substrate such, as a halide or a pseudo halide. Peroxidase-catalyzed oxidation of (pseudo)halides yields

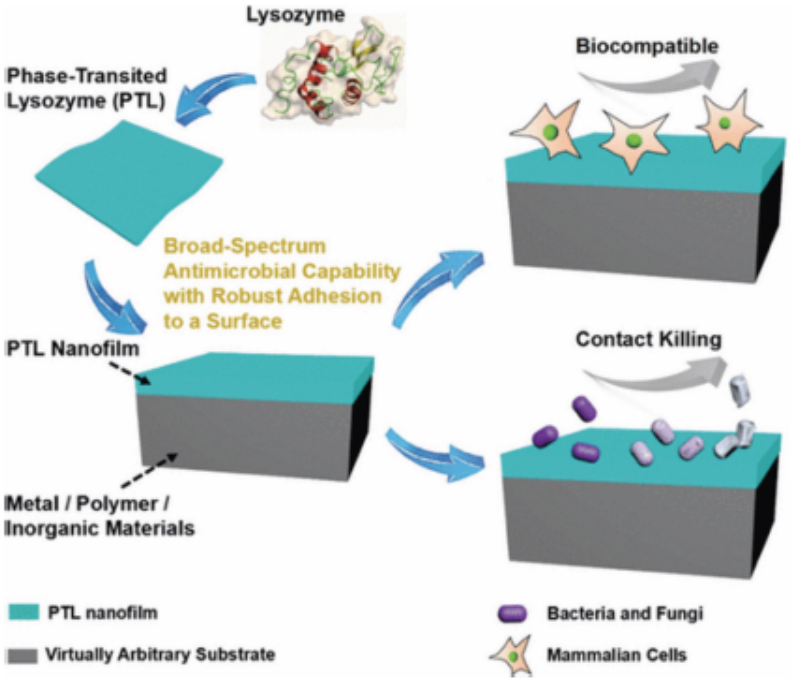

Fig. (15). Strategy to develop phase-transited lysozyme (PTL) nanofilm toward a broad-spectrum antimicrobial coating on virtually arbitrary materials. From Ref [172].

reactive agents which oxidize microorganisms, damaging essential structural and functional components and causing inhibition of microbial metabolism and growth [163].Very recently, novel nanozyme hybrid based on ultrathin graphitic carbon nitride (g-C_3N_4), a non-toxic semiconductors polymer and gold nanoparticles has been proposed [164].The new hybrid provides excellent peroxidase-activity, which can catalyze the decomposition of H_2O_2 to •OH radicals much more efficiently, allowing the use of bio-safety levels of H_2O_2 for the first time. Furthermore, this system not only exhibits striking bactericidal performance against both DR Gram-negative and DR Gram-positive bacteria, but also shows high efficiency in breaking down the existing DR-biofilms and prevents formation of new biofilms *in vitro*. More importantly, *in vivo* experiments indicate that it could significantly prevent bacterial infections and accelerate the healing rate of wounds.

2.4. Antimicrobial Surfaces

Accumulation of micro-organisms on wetted surfaces (bio-fouling) is a multistage process in which cells adhere to a surface by producing an extracellular matrix, typically composed of polysaccharides, proteins and nucleic acids, often surrounding and protecting the micro-organisms and bacteria [165]. Consequently, bio-fouling is the main difficulty impairing the overall performance of polymeric membranes, including selectivity, permeability and long-term stability. The increase of bacterial resistance against common bactericides utilized to inhibit biofilm formation is determining the necessity to develop more efficient antimicrobial membranes. Once a biofilm is formed, it could be difficult or, in some cases, impossible to treat. Strategies based on the release of biocide agents were adopted, showing only a transient efficiency. In this context, nature is again an inestimable source of inspiration to set up strategies against biofilm formation. In particular, Gecko's skin has received great attention for its self-cleaning and super-hydrophobic as well as selective antibacterial properties. It is lethal to Gram-negative bacteria, but not to eukaryotic cells. These features are conferred by its peculiar structure, consisting of small hairs (spinules), separated 0.2-0.7 mm apart and resembling a carbon nanotube forest [166-169].

Therefore, the gecko skin provides a unique topographical template for the design of anti-biofouling surfaces capable to prevent the formation of bacterial biofilm. Recently, superhydrophobic surfaces were prepared *via* the self-assembly of paraffin or fluorinated wax crystals, showing exceptional ability to inhibit biofilm formation of both Gram-positive *Bacillus cereus* and Gram-negative *Pseudomonas aeruginosa* over a 7 day period [170]. Similarly, by utilizing the trapped air cushions or liquid layers, Lotus leaf inspired super hydrophobic surfaces, fish scales inspired underwater superoleophobic surfaces, and *Nepenthes* pitcher plants inspired omniphobic slippery surfaces were successfully designed and tested as anti-biofouling surfaces [171], showing an effectively resistance against bacteria and marine organisms. A large variety of molecules are usually chosen to produce bio-inspired anti-fouling films. Peptides and proteins are very used to realize antimicrobial coatings thanks to their aptitude to form supramolecular structures, bringing to green biomaterials with high antimicrobial activity and low environmental impact. A self-assembled nanofilm by egg white lysozyme was recently produced, showing durable *in vitro* and *in vivo* broad-spectrum antimicrobial efficacy against Gram-positive/negative and fungi [172] (Fig. **15**).

The synergistic combination of positive charge and hydrophobic amino acid residues enriched on polymeric aggregates in the lysozyme nanofilm determined an enhanced

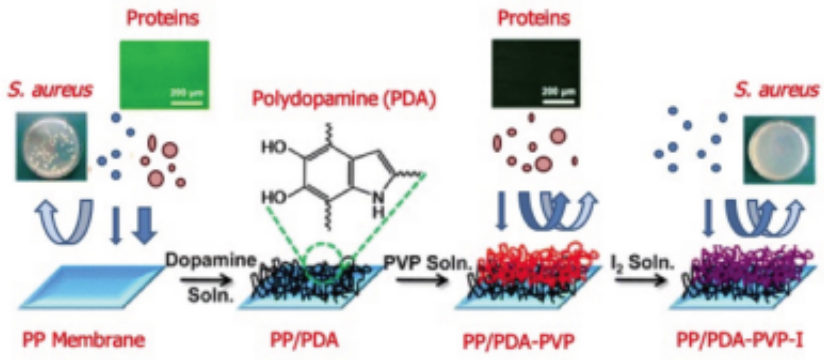

Fig. (16). Schematic illustration of the preparation of antifouling and antimicrobial polymer membranes on the basis of bioinspired polydopamine (PDA). From Ref. [183].

antimicrobial activity. Alternatively, hydrophobic antimicrobial peptides were immobilized into a multilayer film constructed through the enhanced layer-by-layer assembly of polyethylenimine (PEI) and poly(acrylic acid) (PAA). These constructions efficiently killed Gram-positive bacteria *Staphylococcus aureus* including the methicillin-resistant type through a contact-killing mode [173]. Proteins-based antifouling surfaces were also combined with polymers [174] and inorganic materials [175] to realize hybrid surfaces with increased properties in terms of structural resistance and biological performances. Organic–inorganic multilayered films also represent an interesting alternative to classic antifouling films. In this context, architectures similar to nacre were developed basing on bioactive glass nanoparticles, chitosan and hyaluronic acid modified with catechol groups [176]. These multifunctional mussel-inspired multilayered films combined enhanced adhesion and bioactivity, thus they have been proposing as coatings of a variety of implants for orthopedic applications [176].

As also described in the previous paragraphs, polydopamines have been strongly attracting the scientific interest as bio-inspired macromolecules to produce antimicrobial nanostructures. Recently, many studies have described the use of polydopamine for the realization of anti-fouling surfaces. Indeed, polydopamine coatings afford high versatility due to their capabilities to provide substrate-independent functionalization with a wide range of amine- and thiol-containing molecules. Because of its universal adhesive property, this coating strategy was applied to inorganic (*i.e.* TiO_2, SiO_2 and ZnO) [177, 178], metals (*i.e.* Au, Ag and Cu) [179, 180] and organic (*i.e.* polystyrene, polydimethylsiloxane, polysulfone and poly-N-vinyl pyrrolidone) substrates [181-183], bringing to surfaces with a clear superhydrophilicity and excellent fouling resistance against common Gram-negative and Gram-positive bacteria (Fig. **16**).

Finally, the increasing demand to develop novel and environmentally friendly antifouling surfaces induced researchers to select macroalgae as platforms for bioinspiration [184] and to obtain antimicrobial bacterial cellulose membranes by chemical grafting of aminoalkyl groups onto the surface of its nanofibrillar network, mimicking the intrinsic antimicrobial properties of chitosan. Interestingly, these novel grafted bacterial cellulose membranes resulted simultaneously lethal against *Staphylococcus aureus* and *Escherichia coli* and nontoxic to human adipose-derived mesenchymal stem cells, proposing them as film for biomedical application, such as coatings for orthopedic implants [185].

CONCLUSIONS AND PERSPECTIVES

Poor efficacy of conventional antimicrobial therapies against antimicrobial resistance creates the need for new strategies to tackle bacterial infections. In this scenario, combining bioinspired approach with nanotechnology can provide intriguing solutions.

Actually, defenses of living organisms against pathogens are extremely effective, thus mimicking natural systems in both function and formation process, via bio-inspired materials has great potential to make a step-up change the field of sterilization as well as self-cleaning technologies. Therefore, understanding biomimetic materials and their mechanism of action are research areas moving forward.

Research in bio-inspired design using nanotechnology for developing antimicrobial materials is still at the beginning, but it is rapidly advancing with new classes of smart antimicrobial systems being designed.

Bioinspired synthesis relies on safe, non-toxic and eco-friendly processes. Mild synthesis conditions as well as cheaper precursors than conventional procedures lead to cost savings. Obtained antimicrobial nanostructures are usually multifunctional, multi-component systems, combining multiple mechanisms of action into one platform, thus less prone to develop resistance. Sinergy among different components at the molecular scale usually results in a marked increase of biocide efficacy with respect to bare moieties. This further helps to reduce costs for infection treatment. Furthermore, biocide action can be coupled with relevant biological properties, such as anti-inflammatory and wound healing effects. Bio-based substances obtained from wastes have been emerging as valuable, green source of cost-effective precursors and biosurfactants, thus opening new perspectives in the field of biomass remediation.

Nature also provides inspiration for the design of nanostructured bactericidal surfaces, which proved very effective against bio-film formation and have the potential to be incorporated in many bio- medical and industrial applications as an alternative to conventional bactericidal systems.

However, the level of complexity of these fields is not yet fully understood. Furthermore, main issues related to *in vivo* toxicity and bio-distribution of produced bio-inspired solutions must be addressed, in order to open the way to their employment in the biomedical field. Nevertheless, it is actually complexity of these systems joined with huge potential that make them attractive for future research. It is envisaged that developments in the design, fabrication, optimization, and mechanistic understanding of bactericidal efficacy of bioinspired nanostructured systems offers many opportunities for further investigations and may contribute to define effective strategies against pathogenic drug resistant bacteria.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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