Antimicrobial biomaterials with non-antibiotic strategy

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Abstract: Biomedical implants have revolutionised medicine, while they also increase the risk of implant-associated infection which is one of the most frequent and severe complications accompanied by the application of biomaterials. Since the widespread usage of antibiotics drives the emergence of multidrug-resistant strains, the orthopaedic implant infections are usually hard to treat due to the antibiotic resistance, tolerance and/or persistence of pathogens. Given the growing impact of multidrug resistance, an urgent need has been triggered to develop new types of antimicrobial strategy other than using antibiotics. In this review, the authors highlight the recent progress on antimicrobial biomaterials with non-antibiotic strategies including chemical strategy, physical strategy, and synergetic strategy. The antimicrobial mechanisms of many kinds of non-antibiotic antimicrobial biomaterials are still not fully understood. Researchers gradually found that welcoming microbial cellular adhesion to a lethal surface was a more effective solution than targeting microbial cellular repulsion when designing antimicrobial surfaces. Moreover, there is a popular tendency to make the antimicrobial biomaterials not only kill pathogenic microbes but also facilitate the adhesion and growth of the healthy cell, which means that the next generation biomaterials should possess dual functions of preventing microbial infection together with promoting tissue regeneration simultaneously for biomedical applications.

1 Introduction

Human life quality has been dramatically improved since the discovery of penicillin in 1930s [1] because the antibiotics can effectively eliminate many infections. However, the emergence of antibiotic-resistant bacteria and fungi makes infectious diseases continue to be a dangerous threat to public health globally in the 21st century [2, 3]. For example, Centers for Disease Control and Prevention recently reported that Candida auris (C. auris) is an emerging multidrug-resistant fungus which has caused severe illness in hospitalised patients in many countries, including the United States, Canada, China, Russia, and the United Kingdom, etc. [4]. There are 587 confirmed and 30 probable clinical cases of C. auris infection reported by U.S. as of 28 February 2019 [4]. Currently, 700,000 deaths worldwide each year are attributed to antimicrobial-resistant infections, and this number will increase alarmingly to 10 million by 2050 if this trend is not stopped (Fig. 1) [5]. Additionally, conventional antibiotics also have problems such as solubility, overdose, and cytotoxicity [6].

Biomedical implants have revolutionised medicine, while they also increase the risk of implant-associated infection which is one of the most frequent and severe complications accompanied by the application of biomaterials [7–9]. The implant-associated infections account for 25.6% of all healthcare-associated infections in the USA [10]. Notably, the orthopaedic implant infections are usually hard to treat due to the antibiotic resistance, tolerance and/or persistence of pathogens [9]. Tackling bacterial colonies becomes dramatically more difficult once a biofilm begins to form on implant surfaces [11] because the formed biofilm can shelter the bacteria and encourage persistence of infection [9]. When an antibiotic is applied to a typical biofilm, its bactericidal efficacy is limited to the top layer of biofilm, but cannot effectively influence the bacteria located deeper within the microcolonies [12]. The inability of antibiotics to penetrate into and exert their bactericidal efficacy throughout the whole biofilm could endow the bacteria with antibiotic resistance during long-term use of antibiotics, which is the main reason for the failure of using antibiotics to eliminate the biofilms [13–20]. Moreover, the widespread usage of antibiotics has related to the emergence of infectious diseases caused by multidrug-resistant strains [5].

Given the growing impact of multidrug resistance, an urgent need has been triggered to develop new types of antimicrobial strategy other than using antibiotics. In this review, we highlight the recent progress on antimicrobial biomaterials with non-antibiotic strategies including chemical strategy, physical strategy, and synergetic strategy.

2 Chemical antibacterial strategy

2.1 Metal or metallic cation

2.1.1 Silver (Ag): Thousands of years ago, Ag had already been regarded as an antibacterial agent [6]. Medical history documented that Ag powders were used in the treatment of ulcers by Hippocrates [6]. Nowadays, Ag is widely employed in various biomaterials to endow an antibacterial activity to the biomaterials, although the antibacterial mechanisms of Ag were not fully understood. The most accepted hypothesis is that Ag+ can make DNA molecules lose their replication ability and interact with thiol groups in protein to further inactivate bacterial proteins [21].

Ag-loaded hydroxyapatite (HA): Incorporating Ag into HA which is a popular biocompatible and bioactive biomaterial for bone repairing is an effective strategy to endow an antibacterial activity to HA-based materials. There is an increasing interest in the study of Ag-doped HA for antimicrobial applications in the recent two decades [22–47].

Kim et al. [48] prepared Ag-doped HAs using a wet chemical process with an addition of AgNO3. The Ag-doped HA exhibited obvious antimicrobial effect against Escherichia coli, which was ascribed to the bactericidal effect of Ag+ observed by a dialysis tube experiment [48].
Chen et al. [49] prepared a magnetron co-sputtered Ag-containing HA coating and evaluated its antibacterial activity and cytotoxicity in vitro. The Ag-HA surface could significantly reduce the number of Staphylococcus epidermidis and Staphylococcus aureus compared with Ti and HA surfaces [49]. While there was no significant difference in cytotoxicity between Ag-HA and HA surfaces [49].

Lu et al. [50] studied a nano-Ag-loaded HA coating and overcome a challenge that Ag particles can easily agglomerate in coatings to realise a uniform distribution of Ag particles by employing a pulsed electrochemical deposition method to co-deposit Ag particles and HA simultaneously. The antibacterial and cell culture tests indicated that the Ag/HA composite coating had good bactericidal ability and biocompatibility [50].

Qu et al. [51] successfully deposited uniform Ag/HA composite coatings on the inner pore surfaces of porous titanium substrates by a sol–gel process. The Ag particles uniformly distributed in the coatings without agglomeration and Ag/HA 0.8 balanced the biocompatibility and antibacterial ability very well [51].

Xie et al. [52] prepared bone morphology protein-2 (BMP-2)/chitosan (CS)/Ag/HA composite coatings on titanium surfaces by combining the electrochemical deposition and electrostatic immobilisation. The CS can reduce Ag toxicity while retaining its antibacterial activity and chelate Ag⁺ to make Ag nanoparticles distribute uniformly in the coatings [52]. Sustained release of BMP-2 and Ag⁺ from the coatings was successfully realised, which made the coating possess high antibacterial activity (Fig. 2), good biocompatibility, and excellent osteoinductivity both in vitro and in vivo [52].

Xie et al. [53] employed a two-pulse-steps pulsed electrochemical deposition method to prepare spherical HA and Ag nanoparticles using polypyrrole (PPy) nanoparticles as a template. The as-prepared HA/Ag-PPy coating exhibited good biocompatibility, good osteoconductivity, and high antibacterial activity against both E. coli and S. epidermidis [53].

Li et al. [54] prepared a resilient and flexible CS/silk fibroin (SF) cryogel with Ag and Sr co-doped HA (AgSrHA) by combining a physicochemical hybrid-crosslinking strategy and a freeze-drying method. The AgSrHA/CS/SF cryogel exhibited a long-term effective dual-biofunction of antibacterial ability and osteoinductivity since the AgSrHA crystal lattice could avoid the ion burst release behaviour [54].

Ag-loaded hydrogel: Recently, Gan et al. [55] reported that a plant-inspired adhesive hydrogel has been successfully prepared on the basis of Ag-Lignin nanoparticles triggered dynamic redox catechol chemistry (Fig. 3). Owing to the catechol groups and bactericidal ability of Ag-Lignin nanoparticles, the hydrogel was endowed with good cell affinity and high antibacterial activity [55].
2.1.2 Gold (Au): Au nanoclusters: It is well known that bulk Au is the most noble among the metals, chemically inactive, highly stable [56]. Notably, when the size of Au nanoparticles decreases down to 1 nm or sub-nanometer, these ultra-small Au nanoclusters start to exhibit interesting physicochemical properties [56]. Zheng et al. [56] demonstrated that it is possible to confer wide-spectrum functions to materials through the design and synthesis of such Au nanoclusters.
antimicrobial activity to Au nanoparticles by controlling their sizes to
sub-2 nm (nanocluster range). The Au nanoclusters could kill both
Gram-positive and Gram-negative bacteria, since the ultra-small Au
nanoclusters could better interact with bacteria and then induce a
metabolic imbalance in bacterial cells, which caused an increase of
intracellular reactive oxygen species (ROS) production [56].

Au-loaded HA: Nirmala et al. [57] synthesised the Au nanoparticles
incorporated with HA and systematically characterised it to obtain its
morphology, structure, and thermal properties. The broad-spectrum
bactericidal activity of Au nanoparticles incorporated with HA was
ascribed to the presence of Au [57].

Huang et al. [58] prepared a novel nanocomposite which consisted of
Au-coated HA and alginate polymer. The results suggested that
the antibacterial ability of the nanocomposite was attributed to the
interaction between the nanocomposite and carbohydrates as well
as cell wall-related genes [58].

Banerjee et al. [59] actively impregnated the Au nanoparticles into
the HA pellets by absorption during vacuum filtration. The Au
nanoparticles loaded HA exhibited strong antimicrobial activity
against E. coli and S. aureus, which was attributed to the
membrane damage and ROS-mediated bacterial cell death caused
by the Au nanoparticles [59].

2.1.3 Copper (Cu): Cu nanoparticles: Raffi et al. [60]
synthesised zerovalent Cu nanoparticles with an inert gas
condensation method and assessed the antibacterial activity of
these nanoparticles against a Gram-negative bacterium E. coli in
liquid and solid growth media. The results suggested that the Cu
nanoparticles could adhere to and penetrate through the bacterial
cell wall and Cu2+ ions led to the final death of bacteria by
destroying the bacterial cell wall [60].

Chatterjee et al. [61] studied the mechanism of filament formation and
antibacterial roles of Cu nanoparticles in E. coli. It was
demonstrated that Cu nanoparticles caused multiple toxic effects
including generation of ROS, lipid peroxidation, protein oxidation,
and DNA degradation in E. coli cells [61]. The DNA degradation
was significantly inhibited by the presence of ethylenediamine
tetraacetic acid (EDTA) that was a chelator for divalent metal ions,
which suggested a positive effect of Cu2+ ions on the degradation [61].

Cu-loaded HA: Cu-doped HA has attracted more and more
attention because of its excellent antimicrobial ability [59, 62–65].
Stanić et al. [66] employed a neutralisation method to prepare the
Cu-doped HA which possessed high antimicrobial activity against
pathogen bacteria E. coli, S. aureus, and pathogen yeast Candida
albicans.

Li et al. [67] synthesised Cu substituted HA using the wet
chemical method with ion exchange reaction. The Cu substituted
HA nanoparticles exhibited high antibacterial activity against
E. coli, which was ascribed to the leaching of Cu2+ ions that led to
the bacterial cell lysis [67].

Hadidi et al. [68] prepared HA-Cu nanocomposite coatings on Ti6Al4V substrates using electrophoretic deposition method. The
presence of Cu in HA endowed HA-Cu nanocomposite coating with
good antibacterial activity against E. coli and S. aureus [68].

Ghosh et al. [69] prepared a Cu/HA composite coating by two
consecutive electrolytic reactions. The coatings exhibited Cu
concentration-dependent antibacterial activity against both E. coli
(Gram negative) and S. aureus (Gram positive) owing to the slow
release of Cu2+ ions from the coatings [69].

2.1.4 Zinc (Zn): Zn-loaded HA: Stanić et al. [66] synthesised the
Zn-doped HA by a neutralisation method and systematically
characterise the monophasic nano-sized powders. The quantitative
antimicrobial tests in liquid media clearly indicated that Zn-doped
HA exhibited an effective antibacterial ability against E. coli,
S. aureus, and C. albicans [66].

Thian et al. [70] synthesised a Zn-substituted HA (ZnHA)
containing 1.6 wt% Zn with a co-precipitation method and
obtained single-phase ZnHA nanorods with lengths of ∼50 nm and
transverse dimensions of ∼15 nm. Compared with pure HA, ZnHA
exhibited enhanced bioactivity and effective antibacterial activity
against S. aureus [70].

Wang et al. [71] prepared Sr/Zn-codoped HA porous scaffolds by
an ion-exchange method and a foaming method. Both the ab initio
simulation and experimental results suggested that Sr and Zn could
successfully dope into the HA lattice and then change the lattice
parameters of HA [71]. Additionally, the Zn-doped HA and
Sr/Zn-codoped HA porous scaffolds exhibited excellent
antibacterial ability against S. epidermidis [71].

2.2 Anion

2.2.1 Fluorine (F): F-loaded HA: Biomaterials researchers
show a growing interest in studying the F-loaded HA owing to its

![Fig. 4](image-url) Photographs of agar media with colonies of different bacterial strains after incubation and statistical results corresponding to the survivability of three kinds of bacteria on three types of sample surfaces, FHA, HA, and acid-etched pure titanium

a, b For S. aureus
c, d For E. coli
e, f For P. gingivalis. *, indicates a significant difference at p < 0.05, ** indicates a significant difference at p < 0.01, n ∼ 5. Reproduced with permission from Ref [75]
excellent biocompatibility, bioactivity, and effective antibacterial activity [72–74]. Ge et al. [75] successfully deposited a dense and uniform fluoridated amorphous calcium phosphate (FACP) coating with a thickness of around 200 nm on acid etched pure titanium substrate by an electrochemical deposition method. Heat treatment was employed to transform the FACP to fluoridated HA (FHA) which exhibited much higher antibacterial activity against *S. aureus*, *E. coli*, and *Porphyromonas gingivalis* (*P. gingivalis*) than the pure HA and the acid-etched pure titanium (Fig. 4) [75].

Stanić et al. [76] synthesised nano-sized F-substituted HA samples (80 nm in length, 15–25 nm in diameter) by a neutralisation method and demonstrated that the antimicrobial activity against *Streptococcus mutans* of the samples increased with increasing F concentration.

Nasker et al. [77] successfully prepared FHA with different F concentrations by a hydrothermal method. Both Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacterial strains were employed in an antibacterial assay which showed that the FHA with ∼33% F-substitution possessed effective bactericidal ability [77].

Bai et al. [78] deposited nanostructured FHA coatings on Ti substrates with a suspension plasma spraying method. The FHA coating prepared with low spraying power exhibited relatively high antibacterial activity against *S. aureus*, which was demonstrated by optical density (OD) growth curves and colony-forming unit assays [78].

2.3 Metallic oxide

2.3.1 Zinc oxide (ZnO): Jones et al. [79] reported that ZnO nanoparticles had significantly higher antibacterial ability against *S. aureus* than MgO, TiO2, Al2O3, CuO, and CeO2 nanoparticles. Additionally, the results demonstrated that ZnO nanoparticles had a wide-spectrum antibacterial efficacy against a number of other microorganisms, which might be attributed to the nano-size and the presence of normal visible light [79].

Raghupathi et al. [80] reported that ZnO nanoparticles had a wide-spectrum antibacterial activity against various microorganisms including both Gram-positive and Gram-negative bacteria that were commonly found in environmental settings. The antibacterial activity of ZnO nanoparticles was activated by ambient light rather than UV light and inversely proportional to the size of nanoparticles in *S. aureus* [80]. The antibacterial mechanism of ZnO nanoparticles might involve both the production of ROS and the accumulation of nanoparticles in the cytoplasm or on the outer membranes [80].

Fig. 5  Design strategy of the ultra-tough, recoverable, cell-affinitive, and contact-antibacterial AMD-QCS hydrogel

*a* The chemical structure of QCS

*b* MADA

*c* The structure and function of the hydrogel. Reproduced with permission from Ref. [97]

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Sirelkhatim et al. indicated that ZnO is a bio-safe material which has photo-oxidising and photocatalysis effects on chemical and biological species [81]. ZnO nanoparticles possessed effective antibacterial properties owing to enhanced particle surface reactivity by increasing specific surface area with reducing particle size [81]. ZnO nanoparticles can induce the generation of intracellular ROS which is lethal to bacterial cells [81]. ROSs such as hydrogen peroxide (H$_2$O$_2$), OH$^-$ (hydroxyl radicals), and O$_2$•$^-$ (peroxide) are the major factors for several bactericidal and bacteriostatic mechanisms including bacterial cell wall damage due to ZnO-localised interaction, enhanced membrane permeability, internalisation of nanoparticles due to loss of proton motive force, and uptake of toxic-dissolved Zn$^{2+}$ ions [81].

2.3.2 Titanium dioxide (TiO$_2$): Foster et al. [82] indicated that the photocatalytic properties of TiO$_2$ for disinfection had attracted more and more attention. The photoactivated TiO$_2$ can kill a wide-spectrum of Gram-negative and Gram-positive bacteria, filamentous and unicellular fungi, algae, protozoa, mammalian viruses, and bacteriophage [82]. The antimicrobial mechanism involves the cell wall degradation and the cytoplasmic membrane degradation owing to the generation of ROS such as hydroxyl radicals and hydrogen peroxide, which leads to cellular contents leakage then cell lysis and possibly be followed by complete mineralisation of organisms [82]. Close contact between the TiO$_2$ and organisms makes the killing activity more efficient [82].

2.4 Carbon materials

2.4.1 Carbon nanotube (CNT): Vecitis et al. [83] demonstrated for the first time how single-walled CNT electronic structure (i.e. metallic versus semiconducting) is a key factor regulating the antimicrobial activity of single-walled CNT. The authors proposed a three-step antimicrobial mechanism of single-walled CNT including (i) initial single-walled CNT-bacteria contact, (ii) cell membrane perturbation, and (iii) electronic structure-dependent bacterial oxidation [83].

2.4.2 Graphene-based materials: Hu et al. [84] reported that the graphene oxide (GO) and reduced graphene oxide (rGO) nanosheets possessed an effective antibacterial activity against the growth of *E. coli* and minimal cytotoxicity. They also demonstrated the feasibility to conveniently prepare macroscopic freestanding GO and rGO antibacterial papers from their suspension by a simple vacuum filtration [84]. Akhavan and Ghaderi [85] prepared GO nano-walls by electrophoretic deposition of Mg$^{2+}$-GO nanosheets which were synthesised by a chemical exfoliation method. It was demonstrated that the direct contact between the bacteria and the extremely sharp edges of GO nano-walls caused the bacterial cell membrane damage which resulted in the bacterial inactivation [85]. The rGO nano-walls exhibited higher antibacterial activity than the GO nano-walls, which was attributed to the better charge transfer between the more sharpened edges of rGO nano-walls and the bacteria during the direct contact interaction [85].

Liu et al. [86] compared the antibacterial activity of four types of graphene-based materials which were graphite (Gt), graphite oxide (GtO), GO, and rGO against *E. coli* to better understand their antibacterial mechanism. The GO dispersion exhibited the highest antibacterial activity followed by rGO, Gt, and GtO sequentially under similar incubation conditions and concentration [86]. The proposed three-step antibacterial mechanism included initial
bacteria deposition on graphene-based materials, membrane stress caused by direct contact with sharp nanosheets, and the ensuing superoxide anion-independent oxidation [86].

2.4.3 Fullerene: Li et al. [87] pointed out that several C\textsubscript{60} derivatives showed antibacterial effects [88, 89] and C\textsubscript{60} could also form stable aqueous suspensions of nanoparticles named nC\textsubscript{60} which attracted much attention for their broad-spectrum antibacterial activity [90–92].

Zhang et al. [93] reported a novel fullerene derivative C\textsubscript{70}(ethylenediamine)\textsubscript{8} which exhibited high bactericidal activity against multidrug-resistant super-bacteria and negligible toxicity to mammalian cells. The effective antibacterial ability was ascribed to the unique molecular structure of this novel material [93].

2.5 Organic antibacterial agent

2.5.1 Chitosan: No et al. [94] examined the antibacterial activities of six CSs and six CS oligomers with different molecular weights against four Gram-negative and seven Gram-positive bacteria. The results indicated that CSs possessed higher antibacterial activities than CS oligomers and dramatically inhibited the growth of most of the tested bacteria [94].

Rabea et al. [95] indicated that CS which was a hydrophilic biopolymer could be used as an effective antimicrobial agent against fungi, bacteria, and viruses in accordance with low mammalian toxicity.

Kong et al. [96] indicated that CS had been widely used as an antimicrobial agent either alone or together with other natural polymers due to its nontoxicity, high biodegradability, and effective antimicrobial ability.

2.5.2 Inherent antibacterial hydrogel: Inspired by the mussel adhesion chemistry, Gan et al. [97] prepared a hydrogel by copolymerising methacrylamide dopamine (MADA) and 2-(dimethylamino)ethyl methacrylate and networking with quaternised CS (Fig. 5). Since the reactive catechol groups of MADA can increase the exposure of bacteria to the positively charged groups of the hydrogel, they confer a contact intensified bactericidal activity to the hydrogel [97]. The strong, tough, and recoverable hydrogel possessed the dual functions of promoting tissue regeneration together with preventing bacterial infection for

Fig. 7 Characterisation of black silicon and D. bipunctata wings. Scanning electron micrographs of the upper surface of
a bSi
b Dragonfly forewings at 35,000× magnification demonstrate the surface patterns of the two samples. Scale bars, 200 nm. Micrographs tilted at an angle of 53° (inset) show sharper nanopillars of black silicon distinct from one another and approximately twice the height of those of the dragonfly wing
c Optical profilometry shows the nano-protrusions of bSi
b Optical profilometry shows the nano-protrusions of Dragonfly forewings. Scale bars, 50 mm; inset, 2 mm
e Three-dimensional reconstructions based on a displacement map technique further highlight the differences and similarities of bSi
f Three-dimensional reconstructions based on a displacement map technique further highlight the differences and similarities of Dragonfly forewings. Reproduced with permission from Ref. [103]
wound-healing applications, which was demonstrated by both in vitro and in vivo tests [97].

3 Physical antibacterial strategy

3.1 Natural antibacterial surfaces with micro/nanostructures

3.1.1 Cicada wing: One of the pioneer studies on the cicada wing surface was reported by Ivanova et al. [98] in 2012. The authors indicated that it was the first reported example of a naturally existing surface with nanopillars which exhibited extremely effective bactericidal activity against Pseudomonas aeruginosa [98]. The cicada wing surface could kill individual P. aeruginosa cells within around 3 min, which was attributed to a physico-mechanical effect generated by its specific surface topography alone since the bactericidal ability was retained when the surface chemistry was completely changed (Fig. 6) [98].

Hasan et al. [99] reported that the surface of Clanger cicada (Psaltoda claripennis) wing could kill Gram-negative bacteria but was not bactericidal to Gram-positive bacteria since Gram-positive bacteria has thicker peptidoglycan cell walls than Gram-negative bacteria and are therefore more rigid.

Nowlin et al. [100] were the first to report nanostructure-induced rupturing of a eukaryotic microbe that was Saccharomyces cerevisiae. They demonstrated that Au-coated cicada (annual dog day cicada (Tibicen ssp.)) wing surface possessed an effective bactericidal ability by rupturing S. cerevisiae cells [100].

Kelleher et al. [101] studied the wing surfaces of three different cicadas (Megapomponia intermedia, Aythia spectabilis, and Cryptotympana aguila) to correlate the relationship between the surface nanostructures and their bactericidal abilities. All tested wing surfaces contained a highly uniform nanopillar structure, while significant bactericidal abilities were detected on the wings of M. intermedia and C. aguila species due to the high dead/live cell ratio on their surfaces [101].

Shahali et al. [102] systematically characterised the nanostructures on the wing surfaces of three different Australian species of cicadas (P. claripennis, Aleta curvicaosta, and Palapusota eye). The topographies of the nanostructures varied among the cicada species changed between the membrane and the vein of each kind of wing [102]. The nanopillar arrays on the wing surfaces of all the three cicada species exhibited effective bactericidal activity and good biocompatibility [102].

3.1.2 Dragonfly wing: Ivanova et al. [103] reported that the nano-protrusions on the wing surface of the dragonfly Diplacodes bipunctata generated a mechanical bactericidal effect against both Gram-negative (P. aeruginosa) and Gram-positive (S. aureus and Bacillus subtilis) bacteria, as well as endospores (B. subtilis) with estimated average killing rates of up to ∼450,000 cells min⁻¹ cm⁻² (Fig. 7).

Nowlin et al. [100] indicated that the wing surface of a common sanddragon dragonfly Progomphus obscurus with high aspect ratio nanoscale features generated high cell affinity and high bacterial cell rupturing ability. Both native wing surfaces and gold-coated wing surfaces displayed similar bacterial cell rupturing abilities [100]. This result confirmed that surface chemical composition was not a defining factor for nanostructure-induced bacterial cell rupture [100], which was consistent with the conclusion drawn by Ivanova et al. [98].

To prevent the biofilm formation at the very beginning, the traditional idea to design antimicrobial surfaces focused on the strategy for repulsing microbes [104–106] which was extremely challenging due to the dynamic nature of the surfaces, microbes, and environmental conditions [100]. The discovery of the bactericidal activity of the nanostructured surface of insect wing may revolutionise the design strategy of antimicrobial surfaces. Researchers gradually found that welcoming microbial cellular adhesion to a lethal surface was a more effective solution than targeting microbial cellular repulsion when designing antimicrobial surfaces [100].

3.1.3 Gecko skin: Watson et al. [107] investigated the skin of the box-patterned gecko (Lucasium sp.) which consisted of dome-shaped scales arranged in a hexagonal pattern (Fig. 8). It was demonstrated that the gecko skin exhibited bactericidal ability against Gram-negative bacteria (P. gingivalis) and eukaryotic cell compatibility with human stem cells [107].

3.1.4 Taro leaf: Ma et al. [108] reported that the hierarchical nanostructures on the taro (Colocasia esculenta) leaf surfaces were significantly resistant to bacterial (P. aeruginosa) adhesion under completely wetted conditions. The adhesion force on the edge of an epidermal cell was dramatically higher than that on top of the papilla and the area around it [108]. The resistance to bacterial adhesion and reduced adhesion force were ascribed to the dense nanostructures on the epidermal papilla and the area around it [108].

3.2 Artificial antibacterial surfaces with micro/nanostructures

3.2.1 Micro/nano-pillars: Ge et al. [109, 110] were pioneers to study bacterial responses to regular micro/nanoscale pillar arrays from 2011. Periodic micro/nano-pillar arrays with nine different feature sizes (0.6–20 μm) were fabricated on a Si substrate using the
photolithography and deep reactive ion etching techniques [109, 110]. The Si micro/nano-pillar arrays could achieve a significant reduction of bacterial retention, growth, and proliferation when the feature size was reduced down to a sub-micrometer level (Fig. 9) [109, 110]. The antibacterial mechanism was attributed to a physical confinement effect generated by the micro/nano-piller arrays [109, 110], which was double confirmed by the experimental results of TiO2 micro/nano-pillar arrays [109]. Additionally, the extended Derjaguin–Landau–Verwey–Overbeek theoretical analysis suggested that the anti-adhesive effect of the micro/nano-pillar arrays might be caused by a topography-induced surface hydrophobicity change which is represented by the changes in the interaction free energy of Lifshitz–van der Waals among the micro/nano-pillar arrays with different feature sizes [109, 110].

3.2.2 Honeycomb-like patterns: Yang et al. [111] developed micro-scale honeycomb-like patterns of different sizes (0.5–10 μm) on a single Si platform to evaluate the adhesion and growth behaviours of E. coli and S. aureus which possessed two distinct shapes as rod and sphere, respectively. Compared with the flat surface, the honeycomb-like pattern with a feature size of 1 μm could remarkably inhibit bacterial adhesion, growth, and colonisation, which was attributed to a physical confinement effect (Fig. 10) [111]. Although gravity can facilitate the bacterial adhesion, it does not apparently influence the spatial distribution of the adhered bacteria, which was evidenced by the bacterial behaviours on the surface-up and surface-down samples [111].

4 Synergetic antibacterial strategy
To exert the advantages of different antibacterial strategies, researchers started to combine different ‘weapons’ together to
combat against the pathogenic bacteria. Li et al. [112] designed and prepared hybrid ZnO/polydopamine/arginine-glycine-aspartic acid-cysteine nanorod arrays on the surface of the Ti implant. The nanorod arrays could puncture bacteria but not damage osteoblasts, which caused the death of bacteria and the enhancement of osteoinductivity simultaneously [112]. The in vitro and in vivo results revealed that the nanorod arrays possessed contact-killing bactericidal ability against adherent S. aureus and E. coli, which was attributed to the cooperation of selective physical puncture and released Zn²⁺ ions of the nanorod arrays [112].

Ye et al. [113] fabricated a cicaid and catkin inspired dual biomimetic structure which could simultaneously possess higher bacterial anti-adhesive ability, wider antibacterial range, and longer antibacterial durability. First, the burst release of ZnO nanoslices on the sample surface can kill the pathogenic bacteria chemically on the sample surface can kill the pathogenic bacteria chemically [113]. Then, the dual biomimetic structure will be exposed gradually and begin to exert its physical antibacterial property generated by the special nanoscale topography [113].

5 Summary and prospects

To combat against the ever-growing global threats from drug-resistant pathogenic microorganisms, researchers have devoted great efforts to develop novel non-antibiotic antimicrobial strategies. In this review, we highlight the recent progress on antimicrobial biomaterials with non-antibiotic strategies including chemical strategy, physical strategy, and synergetic strategy. A large portion of studies in this field only reported the antimicrobial phenomena but did not profoundly reveal the antimicrobial mechanisms of biomaterials, which resulted in that the antimicrobial mechanisms of many kinds of non-antibiotic antimicrobial biomaterials are still not fully understood. Researchers gradually found that welcoming microbial adhesion to a lethal surface was a more effective solution than targeting microbial cellular repulsion when designing antimicrobial surfaces [100]. Moreover, there is a popular tendency to make the antimicrobial biomaterials not only kill pathogenic microbes but also facilitate the adhesion and growth of healthy cell, which means that the next generation biomaterials should possess dual functions of preventing microbial infection together with promoting tissue regeneration simultaneously for biomedical applications.

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