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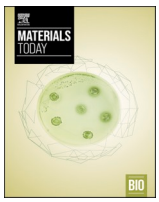

Nature-inspired surface modification strategies for implantable devices

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ABSTRACT

Medical and implantable devices are essential instruments in contemporary healthcare, improving patient quality of life and meeting diverse clinical requirements. However, ongoing problems such as bacterial colonization, biofilm development, foreign body responses, and insufficient device-tissue adhesion hinder the long-term effectiveness and stability of these devices. Traditional methods to alleviate these issues frequently prove inadequate, necessitating the investigation of nature-inspired alternatives. Biomimetic surfaces, inspired by the chemical and physical principles found in biological systems, present potential opportunities to address these challenges. Recent breakthroughs in manufacturing techniques, including lithography, vapor deposition, self-assembly, and three-dimensional printing, now permit precise control of surface properties at the micro- and nanoscale. Biomimetic coatings can diminish inflammation, prevent bacterial adherence, and enhance stable tissue integration by replicating the antifouling, antibacterial, and adhesive properties observed in creatures such as geckos, mussels, and biological membranes. This review emphasizes the cutting-edge advancements in biomimetic surfaces for medical and implantable devices, outlining their design methodologies, functional results, and prospective clinical applications. Biomimetic coatings, by integrating biological inspiration with advanced surface engineering, have the potential to revolutionize implantable medical devices, providing safer, more lasting, and more effective interfaces for prolonged patient benefit.

1. Introduction

Medical and implantable devices play a crucial role in modern healthcare, addressing a wide range of diseases and significantly enhancing patient quality of life. A variety of medical devices are employed in clinical applications, each with distinct implantation sites. Notable examples are pacemakers, which regulate cardiac rhythms; stents, which maintain blood flow in narrowed arteries; artificial joints, which restore mobility; and deep brain stimulators, which treat neurological conditions such as Parkinson's disease [1–10]. In recent years, the scope of implantable technologies has expanded to include advanced systems such as dental implants, deep brain sensors, brain-computer interfaces, electronic pharmaceuticals, biosensors, artificial ligaments, and hip implants. A key consideration in implantable device design is the method of implantation, which varies based on the device's size and function. The implantation of small devices, such as neural sensors and biosensors, is typically performed through minimally invasive procedures. Conversely, the implantation of larger devices, including hip and dental implants, generally necessitates more extensive surgical procedures. Despite the numerous therapeutic benefits of these implantable devices, ensuring their long-term biocompatibility, reliability, and stability in living organisms remains a formidable challenge. The surface of the implant is of paramount importance, as it is the primary interface with the host environment, influencing immune responses, bacterial adhesion, and tissue integration. These factors play a crucial role in the long-term effectiveness of the device [11–13].

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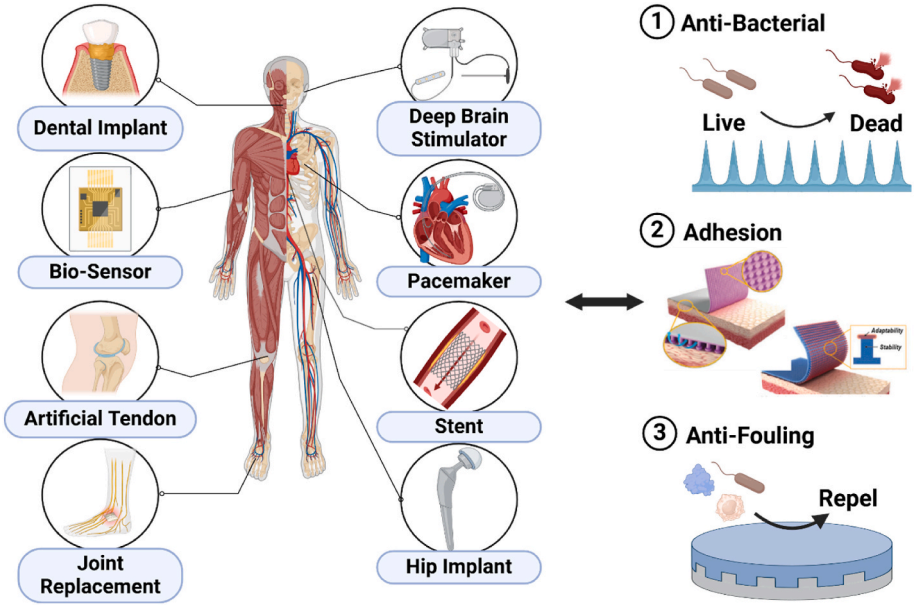

Fig. 1. Summary of nature-inspired surface for implantable devices. Nature offers novel strategies for functional surface design based on surface structures for implant devices and their applications. Reproduced with permission [43]. Copyright 2011, Wiley-VCH. Reproduced with permission [44]. Copyright 2012, Wiley-VCH.(Figures were created with Biorender.com).

Among the various challenges associated with implantable devices, host immune responses and bacterial colonization are particularly problematic. When an implant is introduced into the body, its surface can serve as a substrate for bacterial attachment, leading to biofilm formation. This poses a serious infection risk and can significantly compromise device functionality [14–16]. Biofilms shield bacteria from antimicrobial agents and immune responses, leading to chronic infections that reduce the efficacy of implants [17,18]. These persistent infections not only increase the likelihood of implant failure but also necessitate additional medical interventions, such as prolonged antibiotic treatment or device replacement. In addition, implantation procedures can induce mechanical stress on surrounding tissues, triggering inflammatory responses and foreign body reactions (FBR) [19–21]. Shortly after implantation, proteins rapidly adhere to the device surface, attracting immune cells—particularly macrophages—that may either promote inflammation or facilitate tissue integration [22,23]. The accumulation of macromolecules and cellular debris on the implant surface fosters an environment conducive to bacterial colonization and biofilm development, further exacerbating inflammation [14,24]. During the FBR, macrophages release cytokines, intensifying the inflammatory response. Prolonged inflammation can result in chronic inflammation, device degradation, and the formation of a fibrous capsule around the implant [21,25,26].

Another critical factor affecting implant performance is adhesion between the device and the surrounding tissue. Poor adhesion can result in device displacement or detachment, compromising mechanical stability and overall functionality while simultaneously provoking additional inflammatory responses [27,28]. Addressing these challenges necessitates the development of surfaces with specialized functional properties, including antibacterial, antifouling, and adhesive characteristics, to ensure the biocompatibility and durability of medical devices within the human body.

Traditional surface modification techniques have aimed to reduce bacterial adhesion and enhance tissue integration. However, these methods frequently exhibit substantial limitations. Specifically, they tend to provide static modifications that degrade over time, lack the ability to respond to dynamic changes in the in vivo environment, and are prone to diminished efficacy due to biofouling and material fatigue [29,30]. Consequently, traditional methods often fail to provide lasting protection against infections and chronic inflammatory reactions. Furthermore, many surface treatments address only a single aspect, such as antibacterial properties, while neglecting critical factors like immunological regulation and dynamic tissue interactions. This narrow focus exposes substantial deficiencies in existing surface modification technologies [31].

To overcome these challenges, researchers have turned to biomimetic coatings, which draw inspiration from natural structures and biological processes. By replicating the precise physical and chemical characteristics found in nature, biomimetic surfaces offer a promising alternative to conventional modification techniques. These coatings can integrate multiple functionalities, including antibacterial activity, dynamic adhesion, and resistance to biofouling, thereby addressing the inherent limitations of traditional surface modifications. For example, the antibacterial functionality is achieved by mimicking the nanoscale patterns observed on dragonfly or cicada wings. These patterns create microtopographies that mechanically disrupt bacterial membranes, physically stressing and rupturing cell walls to prevent colonization. In terms of adhesion, researchers develop dynamic and reversible bonding mechanisms by drawing inspiration from natural examples such as the microstructured suction cups of octopus arms, the hierarchical features of gecko feet, and the robust adhesive proteins present in mussels. This approach allows the coatings to adapt to varying environmental conditions and maintain strong yet controllable adhesion. Additionally, to counter biofouling, surfaces are designed by reproducing features like the structures of shark skin and the superhydrophobic properties of lotus leaves. These designs work by reducing the contact area for contaminants and promoting self-cleaning behavior, thereby minimizing the accumulation of unwanted materials. Collectively, these biomimetic strategies demonstrate how nature-inspired designs can effectively overcome the static nature and limited durability of conventional surface modifications, offering advanced, multifunctional solutions for biomedical applications(Fig. 1) [32–42].

This review explores recent advances in biomimetic surface engineering, focusing on antibacterial, antifouling, and adhesive functionalities, alongside the design strategies and fabrication techniques that underpin these innovations. Furthermore, the clinical applicability of biomimetic surfaces is discussed, highlighting the challenges and future directions required to propel the field forward. By leveraging nature-

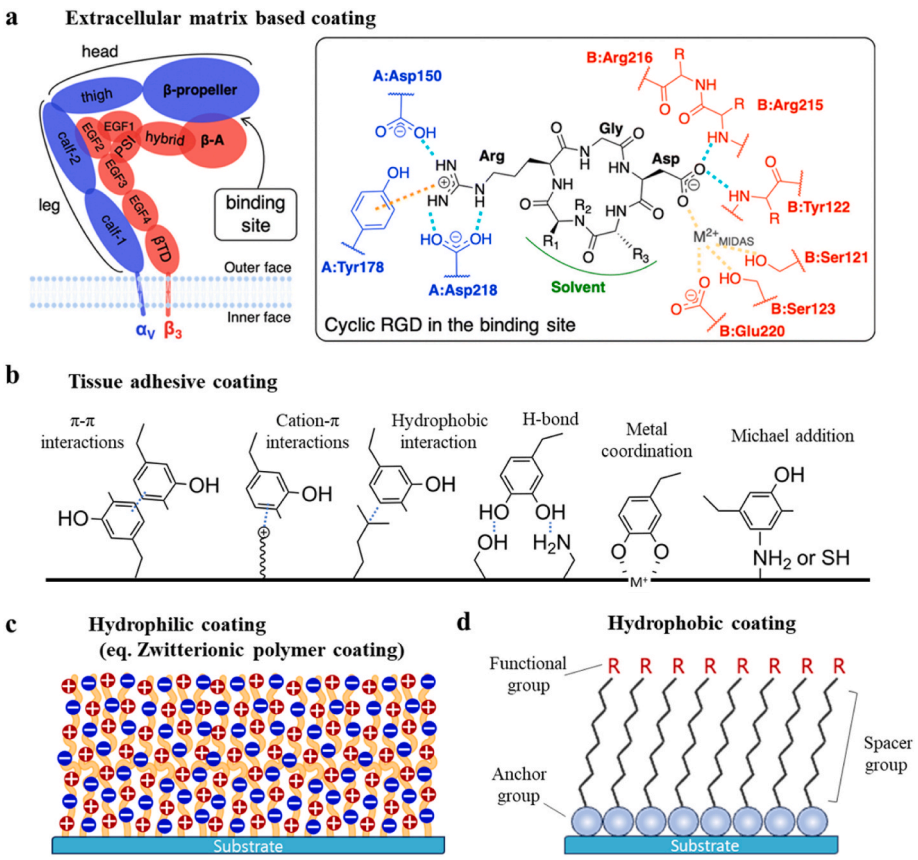

Fig. 2. Representative nature-inspired coating with chemical properties. (a) Schematic illustration of the extracellular segment of integrin $\alpha_V\beta_3$, highlighting the domains of its two subunits that form the binding site (dashed lines). Diagram of a generic cyclic pentapeptide ligand, showcasing its interactions with the integrin $\alpha_V\beta_3$ binding site [57]. (b) Summary of adhesive interactions between catechol groups and various substrate surfaces for tissue-adhesive coatings [58,59]. (c) Schematic representation of hydrophilic surfaces functionalized with zwitterionic polymers. (d) Schematic representation of hydrophobic surfaces fabricated using the SAM method.

inspired strategies, these advancements promise to redefine medical materials, providing safer, more durable, and clinically effective solutions.

2. Chemical and physical perspectives on nature-inspired surfaces

Nature-inspired coatings enhance biocompatibility and durability, providing multifunctional improvements that extend the performance and longevity of biomedical implants. Among various surface modification strategies, chemical approaches based on chemical bonding and reactions, and physical approaches leveraging surface geometries to impart functionality, are often preferred for in vivo applications [45]. This preference is attributed to their lower immunogenicity compared to biological methods, such as protein incorporation. The simultaneous use of physical and chemical strategies can also create multifunctional surfaces that promote synergistic functionalities. This section examines these methods, emphasizing their principles, advantages, and potential for advancing implantable device design.

2.1. Nature-inspired surface using chemical approaches

Chemical surface modification is a pivotal strategy for enhancing the performance and biocompatibility of implants. Chemical approaches use molecular forces such as electrostatic interaction, hydrogen bonding [46], catechol chemistries, and metal ions to impart antibacterial properties [47], cell adhesion, tissue-adhesive [48,49], and also inducing hydrophilicity or hydrophobicity. Since these approaches directly integrate bioactive agents, they are inherently effective in delivering specific functionalities. These chemical modifications tailor implant surfaces to address key challenges, ensuring improved functionality, longevity, and clinical outcomes. This section discusses various chemical coating strategies and their associated functionalities.

2.1.1. Promoting cell adhesion

Extracellular matrix (ECM)-based implant coatings mimic the natural cellular environment, offering a biocompatible and bioactive interface that enhances the integration of implants with surrounding tissues.

The interaction between ECM components and cell receptors is governed by various molecular forces. A key feature of ECM mimics is the incorporation of RGD (Arg-Gly-Asp) peptides, which are critical motifs in ECM proteins [50]. These peptides promote specific cell adhesion by binding to integrin receptors and activating signaling pathways essential for tissue regeneration. This interaction is mediated by several molecular forces [51–53]. First, electrostatic interactions occur between the positively charged arginine (Arg) in RGD and negatively charged residues in the β-subunit of integrins. Second, hydrogen bonding is facilitated by the aspartic acid (Asp) residue in RGD interacting with specific amino acids in the α-subunit. Third, van der Waals forces provide additional stabilization within the integrin binding pocket. Lastly, metal ion coordination at the integrin's metal-ion-dependent adhesion site (MIDAS) involves divalent cations, such as Mg^{2+} or Mn^{2+}, to mediate ligand binding (Fig. 2a). The Asp residue in RGD coordinates with metal ions, further strengthening the interaction and promoting integrin binding. By replicating the native extracellular microenvironment and leveraging RGD-mediated cell

interactions, molecular force-mediated coatings enhance cell adhesion while reducing immune responses. Cationic surface modifications, such as polylysine coatings, are well-known for their effectiveness in promoting cell adhesion and are applied to electrodes [54,55]. Additionally, poly([2-methacryloyloxy)ethyl] trimethyllammonium chloride) (PMTA) has shown promise as a polymer coating, enabling the adhesion and proliferation of glial cells and indirectly supporting the survival of spiral ganglion neurons (SGN) and their neurite outgrowth. Furthermore, anionic coatings on plates have demonstrated enhanced cell adhesion and improved fibroblast morphology when cultured on polyester films [56]. Advances in molecular bonding-inducible coatings, decellularization techniques, and biomimetic fabrication continue to expand the potential of ECM-based coatings, driving innovations in implant performance and achieving improved clinical outcomes.

2.1.2. Enhancing tissue adhesion

Adhesive coatings for implants are designed to enhance the integration of the implant with surrounding tissues by promoting strong and stable attachment at the interface. Catechol-based coatings, inspired by mussel adhesion, form strong covalent, hydrogen bonds and metal-ion coordination, even under wet physiological conditions, ensuring durability. In recent studies, the unique advantages of mussel-inspired catechol and dopamine (DOPA) chemistries to enhance the performance and versatility of hydrogel coatings, have been demonstrated. These naturally derived motifs strengthen crosslinking and cohesion via ion coordination and DOPA oxidation, while residual DOPA groups interact with diverse substrates in aqueous environments (Fig. 2b) [60–62]. Peptides inspired by mussel foot proteins confer several benefits, including persistent adhesion, promotion of osteogenesis, decreased inflammation, and antibacterial and antithrombotic activities [63–66]. One prominent example is mussel-inspired polydopamine or other catechol-containing molecules, which form strong adhesive bonds with metal, ceramic, and polymer surfaces. These molecules cross-link with proteins or other biomolecules, thereby enhancing cellular adhesion and integration [58,67]. Notably, the coordination bonds between metals and catechol groups exhibit non-covalent yet reversible interactions, which simultaneously improve biocompatibility and mechanical strength. This property makes them highly promising for implant coatings and tissue adhesives, particularly in applications subjected to cyclic mechanical loading [68]. This multifunctionality is achieved by integrating antibacterial agents, growth factors, or anti-fouling elements into the adhesive matrix. The versatility, biocompatibility, and functional adaptability of catechol-based adhesives position them as a transformative technology for enhancing the performance and longevity of medical implants [58]. Catechol-based hydrogels are widely applied to various stent materials, offering strong adhesion to implant surfaces along with enhanced endothelialization and antibacterial properties [69,70]. Their robust biocompatibility and anti-inflammatory effects contribute to the long-term stability of implantable devices, ensuring durability and reduced immune response in vivo [71,72]. Li et al. constructed a copper-dopamine (CuII-DA) network with polydopamine (pDA) on vascular stents, resulting in sustained nitric oxide (NO) release, improved endothelialization, and decreased thrombosis and restenosis [73]. Beyond catechol's adhesion capability, π-π stacking interactions between dopamine and hydrophobic chemical drugs, such as doxorubicin (DOX), play a crucial role in hydrophobic drug encapsulation, improving drug stability and controlled release. The study by Kim et al. demonstrates that free dopamine enhances DOX loading efficiency via π-π interactions and hydrogen bonding, which prevents precipitation and improves solubility of hydrophobic drugs. Additionally, the catechol moiety in polydopamine reinforces non-covalent interactions, stabilizing drug-polymer complexes and enabling biocompatible surface functionalization, making catechol-based coatings a promising platform for tissue-friendly, functional implants [74].These examples collectively demonstrate that integrating nature-inspired components, meticulous surface functionalization, and sophisticated fabrication methods can produce hydrogel coatings that improve the mechanical stability, biocompatibility, and therapeutic efficacy of implantable medical devices.

2.1.3. Inducing hydrophilicity

Hydrophilic coatings create a surface that attracts and retains water molecules, forming a hydration layer that provides an environment conducive to integration and long-term performance while minimizing protein adsorption and bacterial attachment [75,76]. Inspired by natural hydrophilic proteins and polysaccharides found on fish scales or mucus layers in living organisms, these coatings effectively resist bacterial adhesion and biofouling [77,78]. They are typically engineered by

Table 1
Summary of nature inspired surface morphologies made of polymer and inorganic materials along with their major properties and application in implantable devices.

	Nature-inspired surface engineering	Major properties	Application in implantable devices
Chemical properties	Cell adhesion able coatings (Extracellular matrix-derived coatings)	Biocompatibility	Cell integration
	Tissue adhesive coatings	Strong covalent bonds Hydrogen bonds Metal-ion coordination	Cell integration
	Hydrophilic coatings	Hydrophilic	Anti-fouling (to prevent protein attachment and bacteria adhesion) [75,84,85]
	Hydrophobic coatings	Hydrophobicity	Anti-fouling (to prevent the protein attachment and bacteria adhesion) [88,89]
Physical properties	A Pillar-like Structure	Hydrophobicity Dry adhesion (10 N–42 N/cm^2) [91,92] Protrusion	Anti-bacterial (Activity: 70 %, toward *E. coli*, and 50 % toward *S. aureus*) [93] Anti-fouling (to prevent the protein and bacteria adhesion, and modulate cell adhesion) [94,95]
	A Crater-like Structure	Hydrophobicity Wet adhesion (3–4 N/cm^2) [96–98]	Cell integration
	A Closely Packed Structure (patterned coating)	Wet adhesion (1.3 N/cm^2) [99]	Cell integration
	A Multilayered Structure	Biologically inert Biocompatibility	Anti-bacterial (Activity: 99 %, toward *S. aureus*) [100] Anti-corrosion
	A thin inorganic layered structure	Biocompatibility Biologically inert Osteoconductive Wear resistance	Anti-bacterial (Activity: Ag cube nanoparticles, 99 % toward *E. coli*) [101] Anti-corrosion Cell integration
	Hydrogel-based 3D structure	Tissue integration Biocompatibility	Adhesion Anti-bacterial (Activity: 99 %, toward *S. aureus* and *E. coli*) [69] Biocompatibility

Table 2
Summary of nano and microfabrication methods along with advantages, disadvantages, and materials range.

	Methods	Advantages	Disadvantages	Scalability	Materials range
Top-down	Optical lithography	High throughput	Resolution limit due to diffraction, High-cost photomasks, complex multi-step process	High	Inorganic and organic
	E-beam lithography	High resolution (<20 nm)	High cost, Slow processing speed,	Low	Mostly inorganic
	Nanoimprint lithography	High throughput High resolution (<10 nm) Low Cost	Mold contamination, Potential defect	High	Inorganic and organic
	Nanosphere lithography	Low consumption High throughput Easy to obtain colloidal crystal	Limited pattern precision, Challenging for uniform assembly	High	Inorganic and organic
Bottom-up	Atomic layer deposition	Easy to control thickness Suitable for large area	High cost, Slow processing speed	High	Mostly inorganic
	Chemical and physical phase deposition	Easy to control thickness Suitable for large area Precise control of film's chemical composition	High cost, Harsh processing (high temperature, toxic precursors)	High	Inorganic, organic, ceramic
	Langmuir-Blodgett	Precise Control Over Layer Thickness Molecular-Level Organization	Poor film stability, Uniformity challenges over large area, Long processing time	Low	Inorganic and organic
	3D printing	Highly customizable and allows for complex geometries	Low resolution, Slow processing speed	High	Inorganic, organic, ceramic

immersing implant substrates into solutions containing specific molecules that spontaneously organize into dense, ordered layers, creating a functional and protective surface [79,80]. Substrate-specific anchor groups, such as phosphonates for metal oxides, silanes for silica, and thiols for gold, ensure strong adhesion and long-term stability under physiological conditions [81–83]. Functionalization with hydrophilic groups or bioactive moieties enhances water retention, charge density, and molecular presentation, further improving the biocompatibility of the coating. The hydration layer formed by hydrophilic coatings acts as a physical and energetic barrier, preventing fouling and immune activation. For instance, zwitterionic polymers, such as trimethylamine N-oxide (PTMAO) derived from trimethylamine N-oxide, mimic natural osmolytes to create highly hydrophilic surfaces(Fig. 2c) [84]. These coatings significantly reduce protein adsorption, complement activation, and cell adhesion by maintaining high water content and stable molecular organization. Additionally, saccharide-functionalized layers engineered with mono-, di-, and trisaccharide head groups provide tunable antifouling properties by regulating molecular packing and hydration [85]. Hydrophilic coatings are particularly effective in enhancing implant biocompatibility and reducing the risk of infection in both in vitro and in vivo settings.

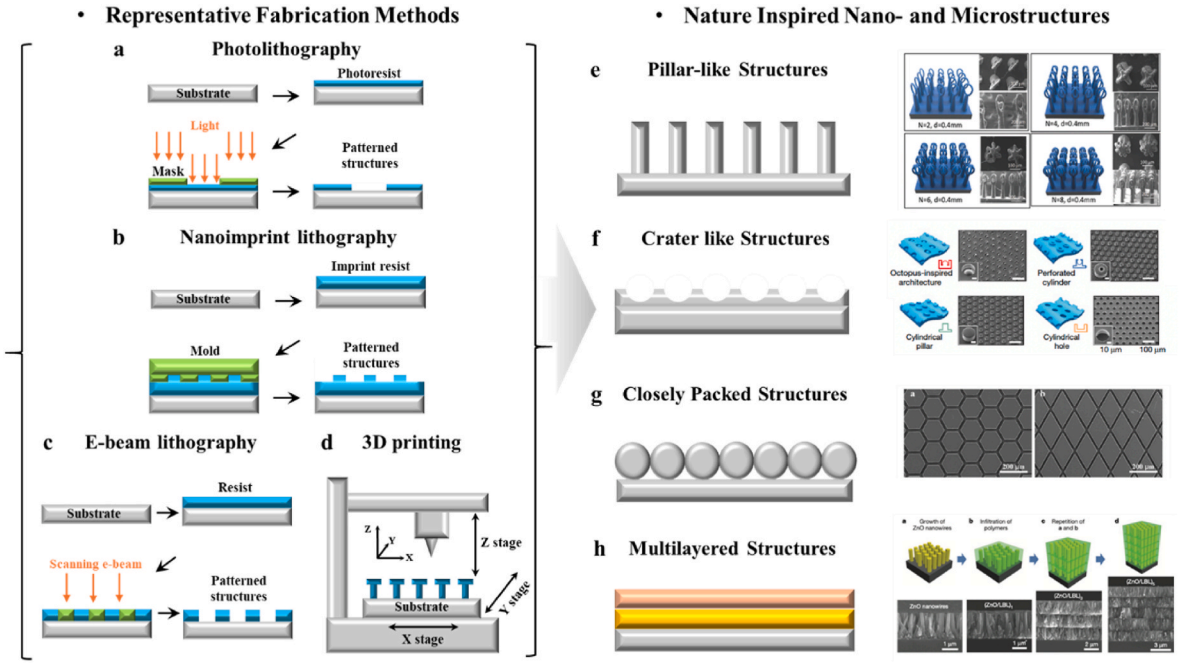

Fig. 3. Representative fabrication methods and nature-inspired nano- and microstructures. (a) a photolithography process, (b) a nanoimprint lithography process, (c) a 3D printing process, and (d) a 3D printing process. (e) the illustration of a pillar-like structure. and SEM images of eggbeater-like nanopillars [110]. Copyright 2017 Wiley-VCH. (f) the illustration of the crater-like structure, and SEM images of cylindrical perforated cylinders and dome-shaped octopus [97]. Copyright 2006 Nature Publishing Group. (g) the illustration of the closely packed structure, and SEM images of hexagonal and rhomboid arrays [111]. Copyright 2015 American Chemical Society. (h) the illustration of the multi-layered structure, and SEM images of multi-layered structures composed of ZnO nanowires and polymers [112]. Copyright 2017 Nature Publishing Group.

2.1.4. Inducing hydrophobicity

Hydrophobic coatings repel water and reduce wettability by minimizing the interaction between water molecules and the surface. They form non-adhesive barriers that inhibit the attachment of biological molecules and microorganisms [86]. These hydrophobic coatings mimic the water-repellent properties observed in natural systems, such as lotus leaves, rose petals, and insect wings [87]. They are fabricated by functionalizing implant surfaces with hydrophobic groups, which reduce surface energy and minimize interactions with proteins and bacteria. The resulting surfaces discourage fouling and biofilm formation, thereby extending the operational lifespan of the implant. The mechanism of hydrophobic coatings relies on reducing water affinity to create a stable, contamination-resistant surface. Advanced molecular design enables precise control over surface hydrophobicity through layer structuring and functional group selection (Fig. 2d). For example, saccharide-functionalized hydrophobic coatings use densely packed structures to repel proteins while maintaining structural stability [88]. The hydrophobic interactions discourage bacterial colonization and reduce biofouling, making these coatings particularly effective for implants used in environments where contamination prevention is critical [89,90]. By mimicking natural antifouling systems, hydrophobic coatings enhance implant performance and ensure long-term durability.

2.2. Nature-inspired surface using physical approaches

This section presents exemplary nature-inspired artificial nano- and microstructures made from inorganic and organic materials, emphasizing their distinctive surface qualities derived from structural characteristics. As illustrated in Table 1, these structures are classified into four categories: (1) pillar-like structures, (2) crater-like structures, (3) close-packed structures, (4) multilayered (5) thin layered inorganic, and (6) Hydrogel-based 3D structures. In addition, fabrication methods along with their advantage and disadvantages are summarized in Table 2.

2.2.1. A pillar-like structure

Pillar-like biomimetic surfaces exhibit unique adhesion properties, with potential applications in adhesives, robotics, and wearable devices. Through the iterative optimization of tip morphology, aspect ratio, and pitch, synthetic surfaces can replicate the hydrophobicity, adhesion, and antibacterial characteristics of natural nanoscale structures [94,95]. Recent advancements in micro- and nanofabrication techniques have further transformed the production of pillar-shaped nanostructures, offering precise control over their geometry and functionality. Photolithography, a widely utilized technique, employs ultraviolet (UV) light to transfer patterns from a photomask to a photosensitive substrate, followed by selective material etching which is a technique to remove certain sites of a substrate to produce the desired features [102–104] (Fig. 3a). For nanoscale resolution, electron-beam lithography (EBL) surpasses the diffraction limit of light, facilitating direct maskless fabrication of intricate structures. However, EBL's slow processing speed limits its scalability for large-scale applications [105,106]. Nanoimprint lithography (NIL) employs pre-patterned molds to transfer nanoscale features onto polymer substrates, supporting high-resolution patterning across large areas [107–109] (Fig. 3b). The scalability and cost-effectiveness of NIL position it as a viable option for industrial-scale manufacturing of nanoscale structures.

Additive manufacturing, particularly 3D printing, has emerged as a transformative approach for fabricating complex structures layer-by-layer (LbL) [113,114] (Fig. 3c). This technique facilitates the production of geometrically intricate designs, including biomedical implants and tissue engineering scaffolds. Recent advancements in high-precision 3D printing have enabled the fabrication of eggbeater-like nanopillar tips exhibiting superhydrophobic properties through LbL photopolymerization [110] (Fig. 3d).

Nanopillars with sharp, high-aspect-ratio characteristics have been fabricated using EBL coupled with reactive ion etching (RIE), allowing precise modulation of tip sharpness and pillar height—critical parameters for achieving bactericidal surfaces [115–117]. The ability to modulate these parameters facilitates the development of surfaces with enhanced antibacterial functionality, a critical aspect of biomedical device design. NIL has also been employed to recreate bio-inspired nanopillar arrays, mimicking the dense arrangements observed in cicada wings [118].

The convergence of bio-inspired design principles with advanced nanofabrication methodologies is driving the development of next-generation multifunctional surfaces. By leveraging the capabilities of diverse fabrication techniques, researchers are unlocking novel applications in fields spanning biomedical engineering and advanced materials science. This interdisciplinary synergy is set to accelerate the development of tailored materials, addressing a broad spectrum of challenges in industrial, medical, and technological domains [119].

2.2.2. A crater-like structure

Crater-like structures can be tailored for diverse applications, including improved adhesion on wet surfaces and enhanced mechanical interlocking at interfaces. These concave geometries, which create localized low-pressure regions upon contact, can be achieved through various advanced micro- and nanofabrication techniques [120–123]. Photolithography combined with reactive ion etching (RIE) enables precise control of cavity dimensions at the nanoscale. In addition, etching techniques—including wet, dry, laser-assisted, and ion beam etching—offer substantial flexibility for shaping complex 3D structures with high precision. Numerous studies have successfully engineered crater-like designs to enhance adhesion under wet and dry conditions [96]. Beik et al. utilized lithographic methods and selective etching processes to fabricate various structures, including cylindrical apertures, perforated cylinders, and dome-shaped, octopus-inspired protrusions [97] (Fig. 3e). Through thorough analysis of adhesion forces in dry, moist, underwater, and greasy conditions, they discovered that dome-like structures created low-pressure chambers upon contact, hence enhancing wet adherence. Min et al. employed micro- and nanofabrication techniques to create wrinkled mushroom-shaped structures featuring microcavities, thereby improving adhesion via the combined actions of suction and capillarity [13]. Lee et al. constructed a double-layered, octopus-inspired structure enveloped in a soft elastomer, showcasing its dynamic adhesive capabilities on uneven, mobile surfaces [98]. By integrating conformal contact with vacuum retention, these manufactured surfaces exhibited strong adhesion to human skin during bending and stretching. Researchers can optimize crater-like nanostructures for enhanced performance under varying settings by employing multiple production methods, including photolithography, reactive ion etching, and specialized etching procedures. Bioinspired designs offer a viable approach for enhancing implantable biomedical devices, facilitating better adherence to moist, irregular, and dynamically altering surfaces within the human body.

2.2.3. A closely packed structure

Close-packed structural arrays enable advanced functionalities such as enhanced wet adhesion, mechanical interlocking, and dynamic adjustability. These precisely arranged geometries mimic natural systems, providing tailored performance for diverse applications. Close-packed structural arrays can be produced using an array of sophisticated patterning and coating methods. Photolithography and subsequent etching techniques facilitate the fabrication of precisely specified polygonal geometries at micro-to nanoscale resolutions, whilst soft lithography technologies, including micro-molding and stamping, enable the replication of complex patterns onto flexible substrates [124,125]. Moreover, nanoimprint lithography and layer-by-layer assembly techniques facilitate the creation of densely packed configurations with exceptional precision and consistency [126,127]. By fine-tuning fabrication parameters—such as feature shape, aspect ratio, and

spacing—these methods enable the creation of patterned coatings designed for improved wet adherence [128–131]. Recent studies have utilized fabrication technologies to examine and enhance the performance of densely packed structures. Chen et al. employed lithographic patterning to fabricate diverse polygonal microstructural geometries (hexagonal, rhomboid, triangular, and quadrangular) and subsequently performed friction force assessments in aqueous environments [111] (Fig. 3f). Their findings revealed that hexagonal patterns provide enhanced wet friction performance, illustrating the direct impact of fabrication-enabled geometric control on functional results. Ruan et al. utilized lithographic techniques to create hexagonal-patterned patches with optimum diameters and aspect ratios, resulting in improved adhesive qualities suitable for rigorous applications [99]. Zhang et al. combined patterning techniques with intelligent hydrogel materials, resulting in hexagonal-patterned coatings that may undergo shape alteration [132]. By regulating the hydrogel's swelling and deformation, these structures facilitated on-demand attachment and detachment from diverse surfaces, demonstrating how innovative manufacturing techniques might provide dynamic, adjustable adhesion properties. These bioinspired, densely arranged structures collectively highlight the significance of manufacturing adaptability. By employing a combination of lithography, imprinting, and pattern transfer processes, one can get precisely engineered coating geometries that replicate natural wet-adhesion mechanisms. Ongoing advancements in these approaches are driving the creation of multifunctional surfaces for biomedical devices, robotics, and other applications requiring robust and dynamic adhesion under challenging conditions.

2.2.4. A multilayered structure

Multilayered structures found in biological systems, such as chameleon skin, nacre, and tooth enamel, exhibit remarkable mechanical and functional properties. Inspired by these natural architectures, advanced fabrication techniques have been developed to replicate and enhance hierarchical designs. Atomic layer deposition (ALD) and chemical vapor deposition (CVD) enable the precise fabrication of nanoscale layers of inorganic materials [133–135]. LbL assembly, spin-coating, and electrostatic spray deposition allow for the spatially controlled placement of organic and inorganic components [136,137]. Additionally, sol-gel processing and dip-coating techniques facilitate the incorporation of organic materials into inorganic matrices, ensuring a cohesive interface and enhanced stress distribution [138]. By leveraging these techniques and adjusting parameters such as layer thickness, composition, and interface chemistry, researchers can create multilayered microstructures that mimic the durability, toughness, and multifunctionality observed in nature [139–141].

Recent advancements highlight the potential of these bioinspired techniques. Yeon et al. utilized LbL and solution-based deposition techniques to distribute ZnO nanowires with polymers, effectively replicating the structure and stress-dissipating properties of dental enamel [112] (Fig. 3g). Similarly, Zhu et al. employed CVD to deposit graphene-dopamine, followed by the incorporation of epoxy resin layers to create a sandwich-like configuration. This structure effectively blocked corrosive substances, significantly enhancing its anti-corrosion performance [142]. Simultaneously, Ziai et al. fabricated multilayered composites by combining fiber mats with plasmonic hydrogel coatings through spin-coating and LbL techniques [100]. This enhanced the composites' mechanical strength and antibacterial characteristics. These studies collectively illustrate that the integration of various fabrication techniques with deliberate material choice and architectural design facilitates multilayered structures that frequently emulate and often exceed the mechanical strength, corrosion resistance, and bioactivity of their natural equivalents. The integration of biomimetic principles and sophisticated engineering technologies presents significant opportunities for the creation of next-generation materials applicable in various industrial, medical, and environmental sectors.

2.2.5. A thin inorganic layered structure

Inorganic coatings play a critical role in enhancing the performance of implantable medical devices, offering improved biocompatibility, mechanical strength, corrosion resistance, and tissue integration. To achieve these properties, advanced deposition processes, such as physical vapor deposition (PVD) [143–145], chemical vapor deposition (CVD) [133–135], electrodeposition [146], and sol-gel processing [147], allow for precise control over coating thickness, content, and morphology. These methods enable the development of stable, homogeneous surfaces capable of withstanding physiological conditions, tailored to meet diverse therapeutic requirements. Within the metallic domain, noble metals such as gold (Au), silver (Ag), copper (Cu), palladium (Pd), and platinum (Pt) are frequently applied as thin films or nanoparticles [148–153] through methods like sputtering, electrodeposition, and evaporation [154]. Au, for example, is incorporated into dental implants and implantable electronics due to its excellent biocompatibility, chemical inertness, and corrosion resistance. Similarly, Ag's potent antibacterial effect, driven by the controlled release of Ag ions that disrupt bacterial metabolism, makes it a popular choice for infection prevention [101]. Cu and Zn-based coatings, often produced via electrodeposition or sol-gel routes, also provide sustained antibacterial activity over extended periods, offering long-term protection against pathogenic colonization [155].

Ceramic coatings, produced using techniques like plasma spraying, electrophoretic deposition, and dip-coating, are widely used in orthopedic and dental implants. Bioinert ceramics such as Al_2O_3 and ZrO_2 exhibit remarkable chemical and mechanical stability in physiological environments, supporting mechanical fixation and promoting osteointegration through fibrous capsule formation [156]. On the other hand, bioactive ceramics like hydroxyapatite can be tailored through sol-gel processing and thermal treatments to release ions that bond with bone minerals, promoting regeneration and more direct bone-implant integration. By adjusting their composition, it is possible to modulate a ceramic's bioactivity and resorbability, ensuring that devices meet the specific needs of patients and clinical scenarios. Collectively, these examples highlight how inorganic coatings, combined with sophisticated deposition methods and compositional adjustments, yield implantable devices that are more robust, biocompatible, and functionally versatile.

2.2.6. Hydrogel-based 3D structure

Hydrogel coatings for implants offer a versatile and biocompatible solution to enhance implant functionality and integration with surrounding tissues. These coatings are hydrophilic networks capable of retaining large amounts of water, mimicking the ECM and creating a bioactive interface [157]. The modulation of hydrogel stiffness to minimize mechanical mismatch with native tissues has emerged as a cornerstone of innovation in tissue engineering and regenerative medicine [158]. Recent advancements have demonstrated the importance of tailoring hydrogel mechanics to closely replicate the elastic properties of target tissues, thereby enhancing compatibility and functionality [159]. Biodegradable hydrogels designed for tissue expanders exemplify this approach, leveraging controlled swelling and degradation to align with tissue stiffness and reduce mechanical discrepancies [160–162]. Alginate-based hydrogels with tunable stiffness reveal the pivotal role of mechanical properties in governing cell behavior, including adhesion and proliferation [163,164]. In neural applications, hydrogels engineered to match brain tissue mechanics minimize foreign body responses, enabling stable and long-term integration in brain-machine interfaces [165,166]. Similarly, multifunctional hydrogels combining polyvinyl alcohol and polyacrylic acid highlight the versatility of stiffness modulation in achieving tissue-like properties, with applications spanning bioadhesives and implantable scaffolds [167]. Chitosan-based hydrogels mimicking neural tissue mechanics further illustrate the utility of precise stiffness tuning in supporting neural regeneration [168]. Collectively, these studies underscore the transformative impact of stiffness modulation in hydrogels, offering a powerful strategy to

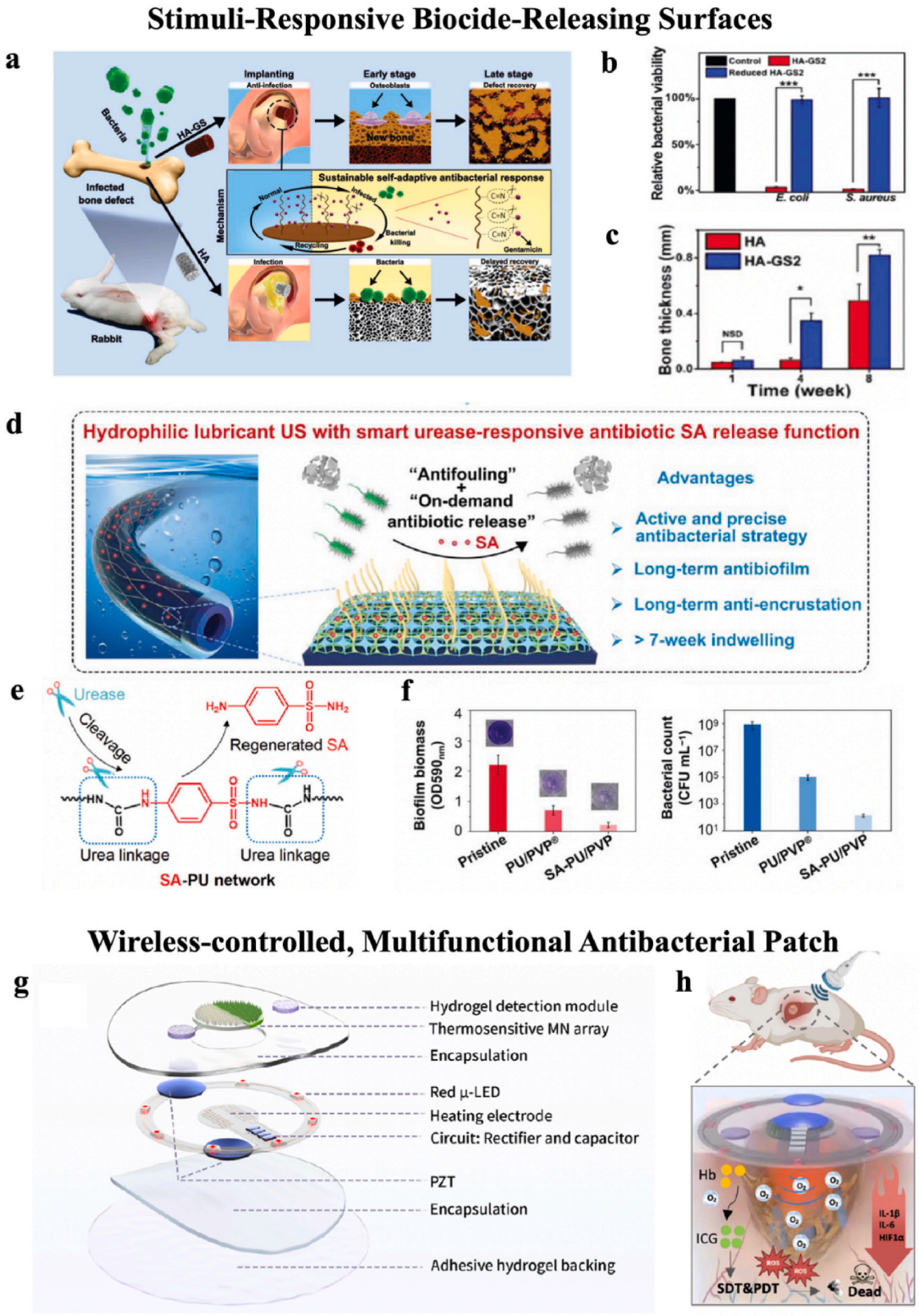

Fig. 4. Implantable devices for chemical antibacterial activity. (a) Schematic illustration of the self-adaptive antibacterial HA–GS implant with sustained responses, (b) Antibacterial activity against *E. coli* and *S. aureus* with and without reduction, (c) Quantitative analysis of bone thickness [182]. Copyright 2019 Wiley-VCH. (d) Schematic of SA-PU polymer-based antibacterial strategy for long-term antibiofilm and anti-encrustation effects, (e) Mechanism of urease-responsive on-demand antibiotic release from the SA-PU/PVP coating, (f) Biofilm biomass and bacterial count on pristine US, PU/PVP-coated US, and SA-PU/PVP-coated US after a 30-day in vitro urine flow model [183]. Copyright 2024 Wiley-VCH. (g) Exploded view of the implantable antibacterial patch with microneedle and piezoelectric transducer, (h) Schematic of the wireless antibacterial patch mechanism for PLA treatment [184]. Copyright 2024 Elsevier.

bridge the mechanical gap between synthetic materials and biological tissues, thereby advancing the field of regenerative medicine.

2.3. Translating biomedical devices to clinical application: alternative and sustainable solutions

The transition of biomedical devices from laboratory experiments to clinical applications is of paramount importance. This transition necessitates not only technological advancements but also sustainable fabrication processes. As described in Section 2.2, several U.S. FDA-approved biomedical devices have already been implemented in clinical applications, including orthopedics, dentistry, fracture management, and cardiovascular medicine [169–171]. Despite considerable progress in fabrication techniques, several limitations continue to impede the clinical translation of biomedical implants, particularly with regard to processing speed, resolution, and scalability. For instance, e-beam lithography facilitates the formation of nanoscale patterns but is characterized by slow patterning speeds, rendering it ill-suited for large-scale production. Similarly, while chemical vapor deposition (CVD) and physical vapor deposition (PVD) techniques permit large-area fabrication, they necessitate high costs due to the requirement of harsh processing conditions, such as elevated temperatures and vacuum environments. The advent of 3D printing has garnered considerable attention due to its capacity to produce complex 3D structures from a diverse array of materials. Nevertheless, its comparatively low resolution persists as a substantial impediment. In order to overcome the aforementioned limitations and enhance the clinical feasibility of biomedical devices, the integration of multiple fabrication methods has emerged as a promising strategy. By combining different fabrication approaches, researchers can leverage the strengths of each method while mitigating their weaknesses, thereby creating a versatile platform for biomaterial fabrication. In particular, hybrid fabrication techniques have been shown to enhance surface functionality in implantable biomedical devices. For instance, to improve the degradation resistance of porous implantable structures, a dip-coating process was employed to coat the tannic acid onto entire surface of 3D-printed porous AZ91 Mg alloy scaffolds, thereby effectively reducing their degradation rate [172]. Similarly, to achieve precise surface patterning with nanofibers, electrospinning was used to deposit nanofibers onto the surface of a 3D-printed mandrel. This resulted in patient-specific TEVGs with mechanical strength comparable to native inferior vena cava (IVC) [173]. As fabrication technologies continue to evolve, hybrid approaches will further improve the clinical applicability of biomaterial devices, rendering them more scalable, functional, and cost-effective.

In parallel with technological advancements, environmental impact and sustainability have emerged as critical factors that must be addressed in both fabrication processes and material selection. Many nanofabrication techniques, such as lithography, etching, and deposition, require high energy consumption, contributing to a significant carbon footprint. Additionally, these processes predominantly rely on petrochemical-based materials, which are often toxic and non-reusable, posing further environmental concerns. In an effort to address the identified challenges, there have been concerted efforts to promote a circular economy system based on three key principles: reduce, reuse, and recycle [174,175]. A promising strategy to enhance sustainability is to substitute conventional petrochemical materials with bio-based polymers derived from recycled materials, low-carbon feedstocks, or renewable natural resources [176,177]. This shift can improve material renewability and reduce the carbon footprint of fabrication processes. Moreover, integrating bio-based materials with additive manufacturing offers a significant opportunity to further contribute to sustainable production. For instance, the integration of additive fabrication techniques, such as 3D printing, with bio-based materials that are sustainable allows for the utilization of reusable resources and waste streams as feedstock for biomaterial production. This approach ultimately facilitates the development of biodegradable and recyclable biomaterials, promoting a more sustainable and eco-friendly future in biomedical fabrication [178].

3. Applications of surface modifications in implantable devices

3.1. Surface modification for antibacterial activity

Antibacterial coatings for implantable biomedical devices have emerged as a transformative strategy to prevent infections by targeting bacterial colonization and biofilm formation. Chemical modifications, such as responsive biocide-releasing surfaces, enable the controlled release of antibiotics or reactive agents in response to bacterial activity, reducing the risk of resistance and cytotoxic effects [179]. Alternative non-antibiotic approaches, including silver-ion systems and photothermal coatings, enhance antibacterial efficacy while addressing concerns about drug resistance [180]. Physical designs inspired by nature, such as nano- and micropillar architectures, provide bactericidal effects through mechanical disruption of bacterial membranes while simultaneously improving tissue integration [181]. These advanced coatings significantly enhance implant durability, support recovery, and elevate the success of biomedical devices.

3.1.1. Antibacterial activity through chemical approaches

In the early stages of research, numerous studies reported the combination of antibiotics with nature-inspired materials or structures and their subsequent applications within the body. Jin et al. developed self-adaptive antibacterial implants for treating infected bone defects [182] (Fig. 4a). The implant is composed of porous hydroxyapatite functionalized with poly(glycidyl methacrylate) brushes and gentamicin sulfate, an antibiotic. The antibiotic gentamicin is released in an acidic environment aided by an acid-responsive bond. This allows the creation of a self-adaptive drug-releasing system in vitro (Fig. 4b). In vivo studies on rabbit models demonstrated that the implants effectively prevented infection and promoted bone regeneration in infected bone defects (Fig. 4c). Li et al. designed urease-responsive ureteral stents with a smart antibiotic release coating [183] (Fig. 4d). The antibiotic sulfanilamide-conjugated polyurethane (SA-PU) was synthesized and integrated with polyvinylpyrrolidone(PVP) to form a coating on a stent. The on-demand release of antibiotics from the coated US can be achieved via cleavage of the urea linkage (Fig. 4e). This has been demonstrated in porcine infection model experiments. It effectively prevents biofilm formation, swarming, and encrustation (Fig. 4f).

Concerns about antibiotic resistance have led to a shift towards exploring non-antibiotic strategies. In a recent study, Yu et al. reported the development of a programmable, versatile surface platform that aims to facilitate reliable bone formation under bacterial infection [185]. The platform, made of poly-γ-glutamic acid (γ-PGA)/Ag, has been shown to possess strong antibacterial properties, resulting from the rapid release of Ag + ions. Ions trigger biological events crucial for bone healing, creating a conducive environment for regeneration. The platform's antibacterial properties, exhibited through the rapid release of Ag + ions, were crucial for bone healing. It achieved osseointegration at the bone-implant interface, mimicking the natural process of implant-associated infection (IAI) healing. Wang et al. reported a near-infrared-responsive, anti-bacterial, and anti-adhesive coating composed of copper sulfide ($Cu_{2-x}S$) nanoparticles and polyethylene glycol (PEG) layer [186]. The PEG layer creates a hydration barrier that resists protein and bacterial adhesion. $Cu_{2-x}S$ efficiently eradicates gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus* under near-infrared (NIR) irradiation. The combination of a non-adhesive surface and NIR phototherapy disrupted bacterial attachment and reproduction, preventing biofilm formation. This approach offers a strategy for developing advanced anti-infective medical devices. Ao et al. developed a hybrid nanostructured surface on polyetheretherketone (PEEK) combining mechano-bactericidal properties with non-antibiotic agents [187]. The nanopillar structure is coated with

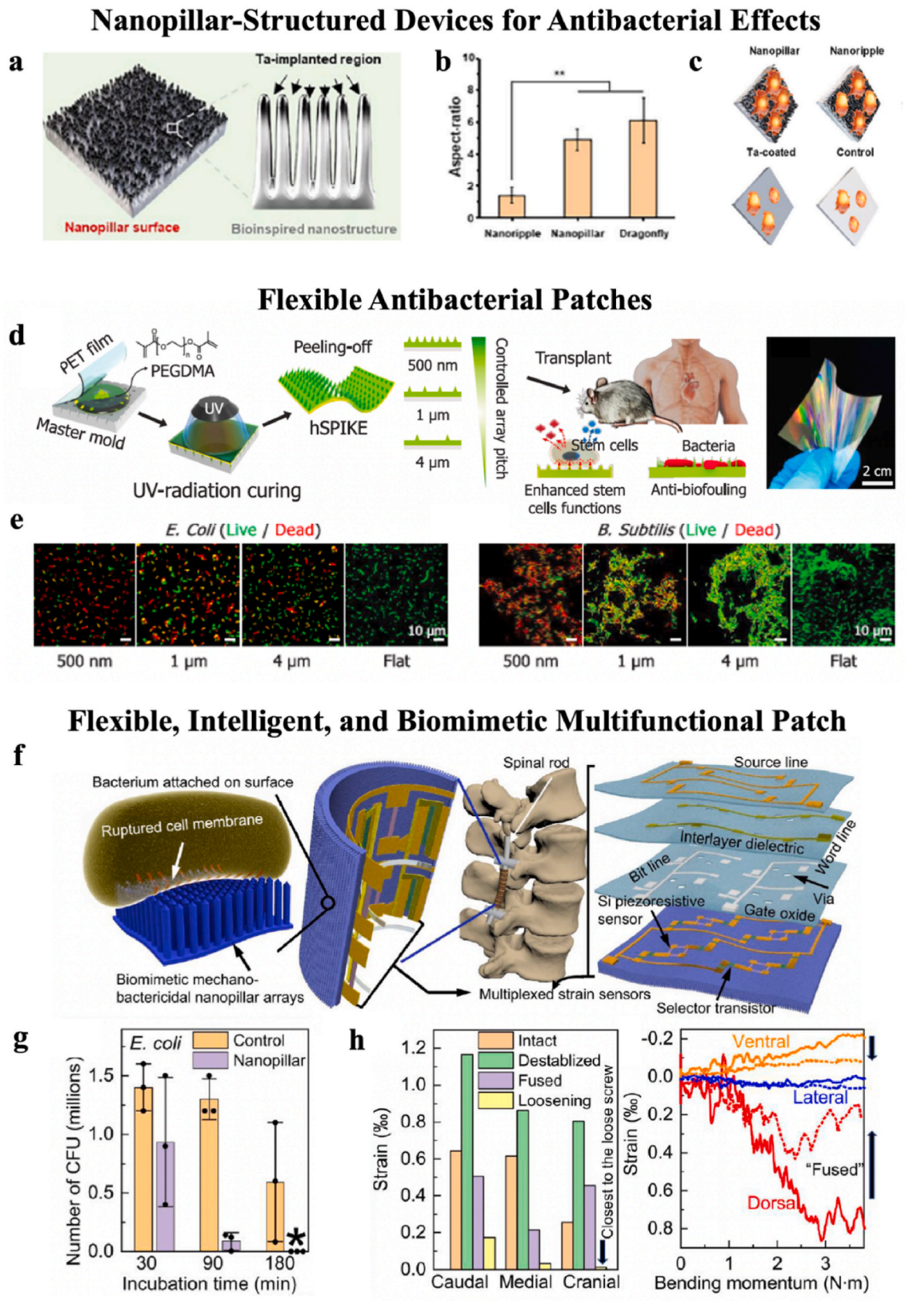

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Fig. 5. Implantable devices for physical antibacterial activity. (a) Structure and functions of nanopillar surfaces for bone implant, (b) Bar graphs comparing form factors between dragonfly wings and nanostructures with different aspect ratios, (*p < 0.05 and **p < 0.005) [93], (c) Schematic and CLSM images showing preosteoblast adhesion on control, Ta-coated, nanoripple, and nanopillar surfaces (the cell nuclei and cytoplasm are displayed in blue and red, respectively). Copyright 2024 American Chemical Society. (d) Fabrication process of hSPIKE patches with pitches of 500 nm, 1 μm, and 4 μm using UV-assisted replica molding, (e) Confocal microscopy images of *E. coli* on hSPIKE surfaces with varying pitches and flat substrates, quantifying live and dead cell coverage [189]. Copyright 2019 American Chemical Society. (f) Design of dual-functional smart-coating foils for orthopedic implants, (g) CFU quantification for *E. coli* strain MG1655 on planar controls (orange) vs. nanopillar arrays (purple) with varying incubation times (up to 3 h, N = 3), (h) Strain measurements by strain-sensing pixels on spinal rods for specimens with intact (orange), destabilized (green), cemented (purple), and pedicle screw-loosened (yellow) facet joints. Strain comparison by pixels in the medial column of spinal rods on ventral (orange), lateral (blue), and dorsal (red) sides during destabilized (solid lines) and cemented (dashed lines) conditions [190]. Copyright 2023 AAAS. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

polydopamine and zinc ions, which disrupt bacterial membranes. This design has been found to target bacteria without harming mammalian cells, offering enhanced bactericidal performance, anti-inflammatory properties, and high biocompatibility. Li et al. developed an innovative ultrasound-driven anti-infection and immunoregulation coating [188]. The coating is activated by ultrasound and comprises three main components: copper-tetrakis (4-carboxyphenyl) porphyrin (Cu-TCPP) for sonodynamic therapy, tinidazole (TNZ) as a hypoxia-responsive antibiotic, and outer membrane vesicles (OMVs) derived from Lactobacillus animalis for immunomodulation. This multifaceted approach integrates anti-infection, immunoregulation, and osteogenesis functionalities, providing a promising strategy for managing implant-related infections and enhancing outcomes in orthopedic surgeries. In a recent study, Chen et al. developed an implantable, wireless-controlled antibacterial patch for eradicating deep abscesses and monitoring therapeutic efficiency [184]. This patch integrates on-demand drug release, light control, and therapeutic monitoring modules (Fig. 4g). Initially, the patch is powered by ultrasound, which releases hemoglobin to alleviate hypoxia and indocyanine green for sonodynamic and photodynamic hybrid therapy (SDT/PDT) (Fig. 4h). In vitro and in vivo experiments have shown that they can eradicate pyogenic liver abscesses, suggesting they can treat other deep infections too.

3.1.2. Antibacterial activity through physical approaches

Nature-inspired nano- and micropillar structures have been developed to eliminate bacteria on the surface of biomedical devices. Lee et al. designed a tantalum (Ta)-incorporated cobalt-chromium (Co-Cr) nanopillar structure inspired by dragonfly wings, providing a dual-function solution to the challenges of bacterial infection and implant integration [93](Fig. 5a). The resulting Ta-coated Co-Cr nanopillar surface showed a higher bactericidal effect, approximately 70 %, toward E. *coli*, and 50 % toward *S. aureus*, compared to the nanoripple surface because the high aspect ratio (6.1 1.4) of the pillars (Fig. 5b). In addition to its antibacterial properties, the Ta-coated nanopillar surface with enhanced hydrophilicity also promoted preosteoblast activity on medical implant (Fig. 5c).

Choi et al. designed an intraocular lens with a polymeric nanopillar array to prevent bacterial infection and postoperative outcomes [191]. The nanopillar array is coated with a copolymer of 4-vinylbenzyl chloride (VBC) and 2-(dimethylamino)ethylmethacrylate (pVD). Quaternary ammonium compounds in pVD enhance electrostatic interaction between nanopillar array (NPA) and bacteria, achieving 99 % antibacterial efficiency against *S. aureus*. This prevents postoperative complications from bacterial contamination of the intraocular lens following cataract surgery.

Flexible patches' adaptability to tissue is in high demand. Park et al. fabricated the transplantable nanotopographic planform, a vertically aligned hydrogel nanospike array (hSPIKE), in the form of a highly flexible patch that not only induces bactericidal effects but also enhances stem cell capabilities [189] (Fig. 5d). Among the hSPIKEs with different designs, the one with a 500 nm pitch exhibited the highest in vitro antibacterial performance against *E. coli* and *Bacillus subtilis* bacteria (Fig. 5e), as well as suppressing pathogenic bacterial infections in mouse models.

Yi et al. developed a flexible intelligent biomimetic patch for biomedical devices, which enhances antibacterial efficacy using synergistic properties of nanopillared surfaces and low-voltage electrical stimulation from triboelectric nanogenerator (TENG) [192]. The biopatch demonstrated significant bactericidal efficiency, reducing bacteria such as *E. coli*, *S. aureus*, *S. epidermidis*, and MRSA by over 99.8 %. This enhanced bactericidal efficacy is attributed to the synergistic effect of mechanical damage induced by nanopillars and electrical stimulation, which has been shown to increase intracellular reactive oxygen species (ROS) levels, thereby rendering cell membranes more susceptible to penetration. In addition, the biopatch is employed as an inflammation indicator by quantitively monitoring temperature changes of *S. aureus*-infected wounds in mice.

More importantly, bio-inspired Janus implantable patches are being developed. These patches can fulfill dual or multifunctional properties. Zhang et al. designed a smart polymer foil coating compatible with commercial orthopedic implants. This coating prevents both septic and aseptic failures [190]. The outer surface of this coating incorporates high-density nanopillar arrays, while the inner surface contains a multiplexed strain-sensing array (Fig. 5f). Applying the foils to orthopedic implants in preclinical models achieved 99 % bacterial clearance and enabled strain mapping for detecting bone fusion and implant loosening (Fig. 5g &h). This dual-function solution addresses both septic and aseptic failures, improving patient outcomes and standard of care. Similarly Liu et al. developed a bioinspired Janus patch featuring a nanopillar structure on one surface and a poly-zwitterion layer on the other for treating abdominal wall defects [193]. This study highlights the Janus patch's dual functionality, with nanopillars exhibiting mechano-bactericidal activity against bacteria while promoting cell adhesion and proliferation for selective biocidal effects. Meanwhile, antibiofouling PSBMA brushes on the bottom surface prevent visceral adhesion, achieving a clinical adhesion score of 0 in a rat abdominal wall defect model. This asymmetric design, integrating antibacterial, anti-adhesion, and pro-healing properties, shows great promise for next-generation internal soft-tissue repair patches.

These examples show a paradigm shift towards multifunctional implant coatings that integrate antibacterial, anti-inflammatory, and regenerative functionalities. These designs enhance the performance and longevity of biomedical implants, advancing the management of implant-associated infections.

3.2. Surface modification for adhesion

Researchers are increasingly focusing on developing nature-inspired implant coatings to enhance cellular attachment and growth, fostering a stable interface between implants and surrounding tissues. This section explores biomimetic approaches to improving cell adhesion and tissue integration on implant surfaces, emphasizing their potential to enhance implant stability and minimize complications.

3.2.1. Adhesion through chemical approaches

Researchers have investigated chemical surface modifications for better implant adhesion and integration with surrounding tissues. These modifications enhance cellular attachment, support tissue growth, and reinforce implant stability. Recent research has focused on responsive surface coatings that adjust their chemical characteristics to

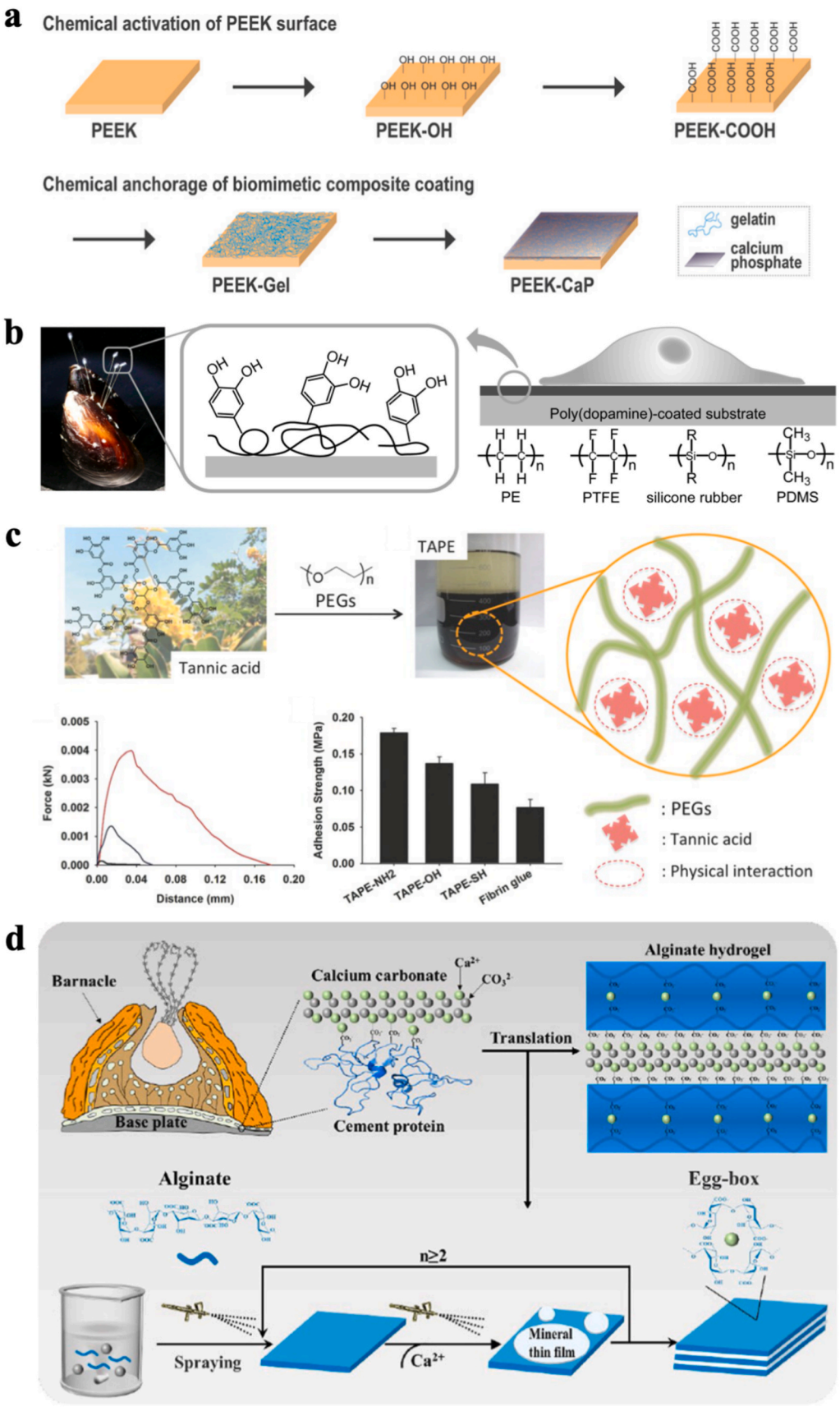

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Fig. 6. Nature-inspired coated on implant for adhesion with chemical properties. (a) Schematic representation of the chemical activation and biomimetic coating of the PEEK implant surface, inspired by natural systems including marine adhesives, lotus leaf antifouling surfaces, and bone-like textures [195]. Copyright 2024 Wiley-VCH. (b) Schematic illustration of cell adhesion on substrates modified by mussel-inspired poly(dopamine) [196]. Copyright 2010 Elservier. (c) Formation of TAPE: Tannic acid (TA), a key component of hydrolysable tannins found in plant secondary metabolites, is mixed with PEG to mass-produce TAPE at a laboratory scale (500 mL). Force–distance curves compare the adhesion strength of TAPE–NH_2 (red) with TA (blue) and PEG–NH_2 (black), while adhesion performance is evaluated for TAPE with various PEG terminal groups (–NH2, –OH, and –SH) alongside fibrin glue as a positive control [197]. Copyright 2015 Wiley-VDH. (d) Barnacles utilize cement proteins to create strong underwater adhesion by binding $CaCO_3$ base plates to foreign surfaces [199]. Copyright 2024 American Chemical Society. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

environmental stimuli. This approach optimizes cell adhesion and tissue integration, providing a safer, more adaptable method for achieving sustained implant performance. Shou et al. introduced dual peptide hybrid coatings, inspired by the ECM, to promote bone regeneration and enhance osseointegration [194]. By grafting RGD and OGP peptides onto metal-polyphenol networks (MPNs), these coatings exhibit bioactive properties, including enhanced cell adhesion, immune modulation, antioxidant activity, and osteoblast differentiation. The osteogenic activity of MC3T3-E1 cells was fine-tuned via the Wnt/β-catenin signaling pathway by optimizing the RGD-to-OGP peptide ratio. In vivo studies in rat models demonstrated significant improvements in bone regeneration and osseointegration, providing a robust framework for functionalizing bioinert implant surfaces in bone tissue engineering. Knaus et al. explored biomimetic coatings inspired by natural systems such as marine adhesives, lotus leaf antifouling surfaces, and bone-like textures (Fig. 6a) [195]. These designs effectively enhance cell adhesion, resist biofilm formation, and support tissue integration, while incorporating responsive materials capable of adapting to environmental changes, regulating drug release, and providing antibacterial effects. Similarly, Ku et al. advanced this approach with coatings that emulate natural structures, demonstrating enhanced biocompatibility, biofilm resistance, and adaptability to dynamic environments, thereby improving implant performance and durability across diverse medical applications (Fig. 6b) [196]. Kim et al. developed a medical adhesive inspired by tannic acid (TA), a natural polyphenol [197]. TAPE is a simple mixture of TA and PEG. It sticks well and can be broken down by the body. It can also stop bleeding and help diagnose GERD. This study shows the potential of TAPE in a range of applications, including medical adhesives, drug delivery, and diagnostics (Fig. 6c). Similarly, Lee et al. developed a catechol-conjugated alginate (Alg-CA) hydrogel coating for the strain-adaptive fiber-interlocked electronic (SAFIE) sensor patch, thereby enabling instantaneous cardiac tissue adhesion and suture-free long-term ECG monitoring [198]. The fatigue-resistant conductive composite enhances tissue-device integration while maintaining functional stability, thus highlighting the potential of biomimetic coatings in advancing implant technology. Liu et al. proposed a novel method inspired by barnacles to enhance the adhesion of multi-layer hydrogels. Adding $CaCO_3$ or $Ca_3(PO_4)_2$ between alginate layers makes it as strong as the adhesive of a barnacle, with stable bonding. This mineralization approach improves hydrogel adhesion to biological surfaces, offering promise for biomedical applications requiring durable tissue integration (Fig. 6d).

Tao et al. developed a polymer-coated β-TCP (beta-tricalcium phosphate) scaffold designed to address challenges in diabetic bone defect repair [200]. Their approach involved immobilizing small extracellular vesicles (sEVs) onto the scaffold using a LbL self-assembly method with hyaluronic acid (HA) and poly-L-lysine (PLL). To enhance surface functionality, the scaffold was further modified with DSPE-PEG-c (RGDfC) and loaded with ZEB1 using optogenetic technology (EXPLOR). This coating strategy significantly promoted angiogenesis and osteogenesis while suppressing overactive osteoclast activity, resulting in improved bone regeneration under diabetic conditions. Choi et al. present the shape-morphing cortex-adhesive (SMCA) sensor, which incorporates a catechol-conjugated alginate hydrogel to enable instantaneous tissue adhesion, artifact-free neural recording, and closed-loop ultrasound stimulation for epilepsy treatment [201]. The biomimetic coating ensures stable bioelectronic interfacing under mechanical stress, demonstrating its potential to enhance implant integration and long-term functional stability. This innovative scaffold exemplifies the potential of biomimetic coatings in advancing implant performance and addressing complex tissue repair challenges. The examples demonstrate the capacity to enhance tissue adhesion while preserving functional properties, suggesting the potential for advancing implant technology.

3.2.2. *Adhesion through physical approaches*

Surface topography plays a critical role in cell adhesion, with nano- and micro-patterned coatings inspired by natural structures in bone and other tissues providing physical cues that guide cellular behavior. These structured surfaces align cells and support tissue formation, contributing to improved implant integration and stability over time. Nature-inspired coatings that mimic the ECM or bio-adhesive proteins offer unique advantages, including enhanced implant performance and reduced risks of complications, demonstrating their transformative potential in biomedical applications. Nature-inspired patterned surfaces enhance and sustain implant performance. Wu et al. designed a switchable adhesive patch for laparoscopic liver retraction, inspired by the suction mechanism of the octopus (Fig. 7a). Mimicking the octopus's sucker rim with polymeric materials, the patch incorporates a temperature-sensitive layer to enable secure liver retraction while minimizing tissue damage. Mechanical and biocompatibility tests validated its efficacy, establishing it as a promising tool for minimally invasive surgeries [202]. Similarly, Min et al. introduced DIA-w, an adhesive patch modeled after the suction cup structures of diving beetles (Fig. 7b) [13]. Featuring wrinkled, mushroom-shaped pillars with microcavities, this design achieves strong wet adhesion and ensures stable attachment to both dry and wet surfaces. Biocompatible and moisture-draining, the patch is suitable for wearable biosignal monitoring devices, offering irritation-free and comfortable use, thus underscoring the potential of insect-inspired designs in medical applications. Building on these concepts, Zhang et al. proposed bioinspired soft robots to improve implant adhesion and enable multifunctional sensing and adaptive actuation (Fig. 7c) [203]. By integrating electronic skin and artificial muscle layers, these devices facilitate wireless, untethered operation, allowing precise and minimally invasive interactions with biological tissues. This nature-inspired approach provides a versatile platform for next-generation medical applications, combining enhanced adhesion, adaptability, and functionality. Collectively, these advancements highlight the transformative potential of biomimetic designs in redefining the capabilities of medical implants and devices.

In summary, Nature-inspired and biomimetic approaches advance implant coating development by enhancing adhesion, tissue integration, and efficacy. These coatings emulate natural structures such as the ECM, marine adhesive surfaces, and bone-like textures, promoting cell adhesion, tissue regeneration, and reducing complications like infection and inflammation. Innovative strategies such as bio-inspired soft robotics, responsive materials and multifunctional scaffolds expand the potential for implant technology, enhancing stability and functionality. These coatings not only enhance implant stability and functionality but also offer adaptable solutions to meet the challenges of complex tissue environments, demonstrating immense promise for the future of implant technology.

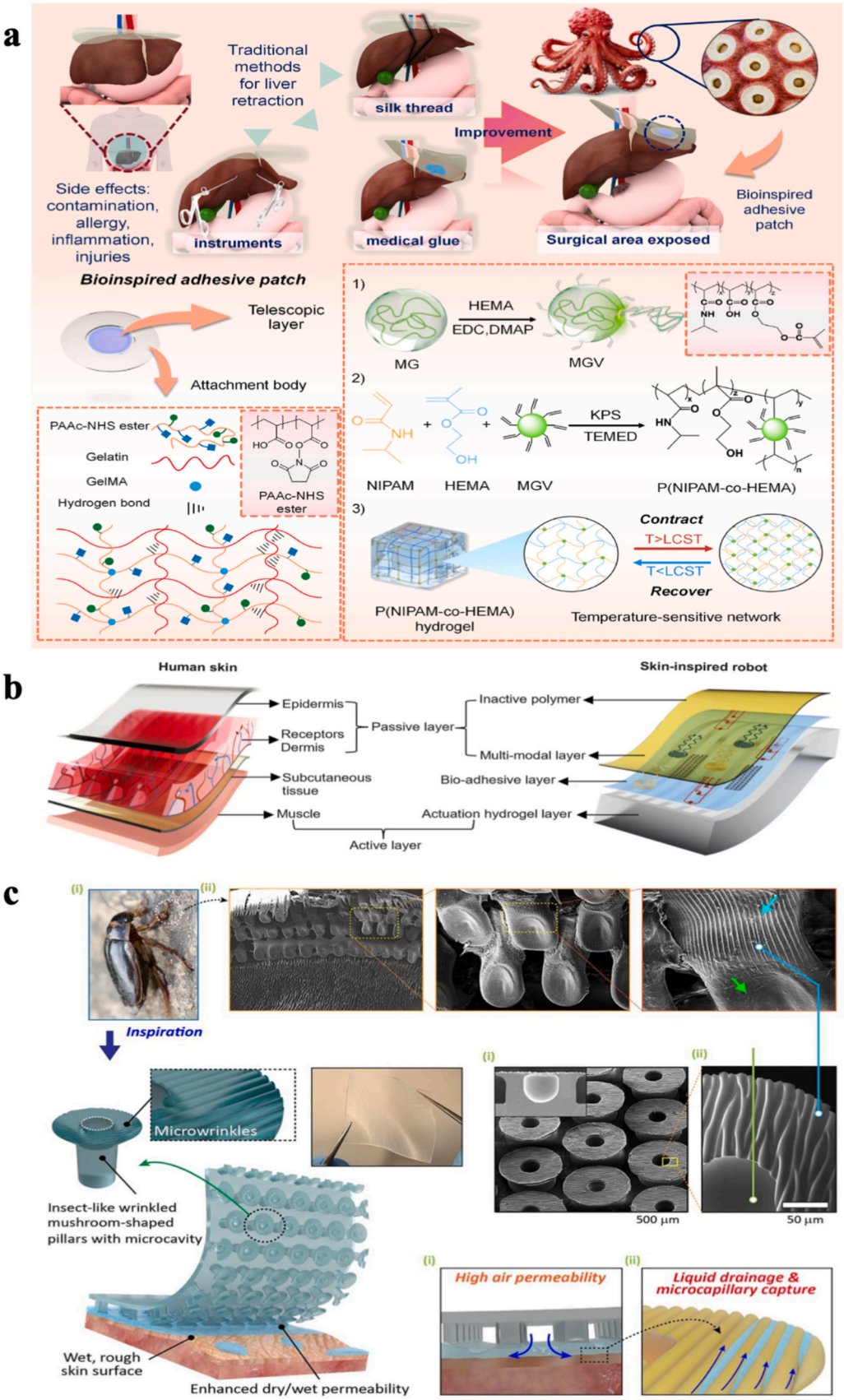

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Fig. 7. Nature-inspired coated on implant for adhesion with physical properties. (a) Design inspiration, strategy, and potential applications of the adhesive patch. Illustration of traditional liver retraction methods in laparoscopic surgery alongside a schematic overview of the bioinspired adhesive patch. Depiction of the components of the adhesive patch, including the synthesis process for the attachment body and the temperature-sensitive telescopic layer [202]. Copyright 2024 Elservier.(b) An adhesive patch inspired by the foreleg structures of male diving beetles, showcasing the design, structure, and functional properties of the DIA-w patch with microwrinkles and mushroom-shaped pillars for improved adhesion, air permeability, and liquid drainage [13]. Copyright 2022 Elservier. (c) Schematic representation of the epidermis-dermis-muscle structure of the skin and the bioinspired design of a soft robot modeled after skin architecture [203]. Copyright 2024 Nature Publishing Group.

3.3. Surface modification for anti-fouling

Efforts to mitigate corrosion and protect implant devices following transplantation have focused on two critical objectives: reducing infection risks and enhancing implant durability to extend their functional lifespan. Advanced strategies, including hydrogels, polymers, coatings, and self-assembled monolayers, have been employed to improve corrosion resistance and establish protective barriers for medical implants. Xue et al. introduced a fatigue-resistant conducting polymer hydrogel coating for metallic bioelectrodes (Fig. 8a). By incorporating nanocrystalline domains at the interface, the study improved the durability of poly(3,4-ethylenedioxythiophene):polystyrene sulfonate (PEDOT:PSS) hydrogels, enhancing resistance to fatigue cracking and delamination. The resulting PEDOT:PSS/PVA hydrogel coating demonstrated exceptional stability, a low pacing threshold voltage, and suitability for long-term bioelectronic applications. This innovation offers a robust platform for personalized and minimally invasive medical treatments [204]. Inspired by the Nepenthes plant, Chae et al. created the Lubricated Orthopedic Implant Surface (LOIS), a coating with a thin lubricant layer embedded in a micro/nano-structured surface (Fig. 8b). The LOIS coating repels liquids and bacteria while maintaining mechanical durability. In rabbit models, LOIS-coated implants significantly reduced infection and inflammation without compromising bone healing, positioning it as a promising solution for high-risk orthopedic surgeries and paving the way for clinical translation [205]. A honeycomb-inspired surface structure effectively minimized thrombus formation by significantly reducing protein adsorption and platelet adhesion [206]. In a one-month rabbit trial, this design showed minimal thrombosis and inflammation, demonstrating its potential as a hemocompatible surface modification. Similarly, femtosecond laser ablation was used to make interconnected porous polymer surfaces with nanoscale pores (Fig. 8c) [207]. Chemical treatment then lowered surface energy and lubrication to create a slippery interface. These surfaces hindered droplet adhesion and cell attachment, improving device performance, safety, and patient outcomes. Wu et al. developed a TA-based zwitterionic polymer coating on glass surfaces to achieve antibacterial and antifouling properties. The process involved forming a silica sol layer, co-depositing TA and 3-aminopropyltriethoxysilane (APTES) to create a hydrophilic layer, and grafting a zwitterionic polyethylenimine-quaternized derivative (PEIS) via Michael addition and Schiff-base reactions. The resulting Glass@Silica Sol-PEIS coating exhibited high hydrophilicity (contact angle 6.3°), strong antibacterial activity (*E. coli* >80 %, *S. aureus* 71 %), and excellent antifouling performance (microalgae adhesion prevention >96 %) [208]. Acosta et al. developed a novel hybrid coating system using protein-engineered elastin-like recombinamers (ELRs) to tether antimicrobial peptides (AMPs) on implantable device surfaces. This ECM-mimicking system exhibited significant antibiofilm activity against mono- and multispecies biofilms, including clinically relevant pathogens. The coatings also demonstrated excellent cytocompatibility with human gingival fibroblasts, highlighting their potential for preventing implant-associated infections (IAIs). These multifunctional coatings combine the antimicrobial potential of AMPs with the tunable properties of ELRs, offering a promising solution for enhancing the biocompatibility and functionality of biomedical implants [209]. Zhang et al. designed bio-inspired poly-DL-serine (PSer) hydrogels, inspired by the high L-serine content in silk sericin and the role of D-serine as a neurotransmitter [210]. Using simple and scalable methods, they synthesized highly water-soluble PSer hydrogels to mitigate the foreign-body response (FBR) in implantable materials. Subcutaneous implantation in mice revealed that PSer hydrogels outperformed poly(ethylene glycol) (PEG) hydrogels in reducing FBR, while promoting vascularization and enhancing nutrient exchange at the tissue-material interface. Similarly, Yang et al. introduced a cell membrane-biomimetic coating to address the FBR often observed with synthetic polymer scaffolds [211]. Their approach utilized electrospun polystyrene fibers as a model, coated with silk fibroin through LbL assembly, followed by covalent immobilization of liposomes via copper-free strain-promoted azide–alkyne cycloaddition (SPAAC) click chemistry. This liposome-functionalized coating significantly enhanced vascularization, reduced inflammation, and polarized macrophages toward a pro-regenerative phenotype in vivo. These outcomes not only improved tissue-material integration but also mitigated FBR, providing a promising solution to enhance the biocompatibility of synthetic scaffolds.

4. Perspective and conclusion

The development of durable and multifunctional biomimetic surface technologies plays a pivotal role in the future of implanted medical devices. While these technologies hold immense potential to enhance biocompatibility, achieving long-term stability remains a significant challenge. Ensuring that surfaces maintain their functionality under diverse physiological conditions requires the design of robust materials and scalable production processes to support widespread clinical application. The demand for multifunctional surfaces capable of simultaneously exhibiting antibacterial, antifouling, and tissue-adhesive properties is steadily increasing. Dynamic or intelligent surfaces that can adapt to physiological changes are considered a promising strategy for achieving multifunctionality, offering adaptive responses to variations within the body. Such surfaces have shown the potential to prevent biofilm formation and mitigate inflammation, thereby promoting more effective interactions between implantable devices and host tissues.

Although current experimental results are promising, most data remain at the preclinical stage, and long-term effectiveness in clinical settings is yet to be fully established. Thus, while biomimetic surfaces have the potential to transform the design and functionality of medical implants, this potential should be viewed as a promising avenue for future research rather than an immediate revolution. As a representative example, developing a data-driven strategy for surface treatment through existing experimental data and computational simulations can significantly enhance the success rate of bioimplantation. The integration of advanced computational tools, such as artificial intelligence (AI) and machine learning has accelerated the design and optimization of biomimetic surface technologies. By enabling the rapid identification of optimal surface patterns and material compositions, these technologies facilitate the development of surfaces with enhanced bacterial resistance, improved tissue integration, and greater durability. AI-driven analysis of large experimental datasets helps uncover key design principles, allowing for the creation of high-performance biomimetic surfaces with superior functionality and adaptability across various therapeutic applications. This computationally guided approach not only improves precision and efficiency in surface engineering but also enhances the clinical feasibility and success of implantable medical devices. The clinical translation of biomimetic surface technologies relies on rigorous preclinical and clinical evaluations, as well as compliance with regulatory standards. Demonstrating safety, biocompatibility,

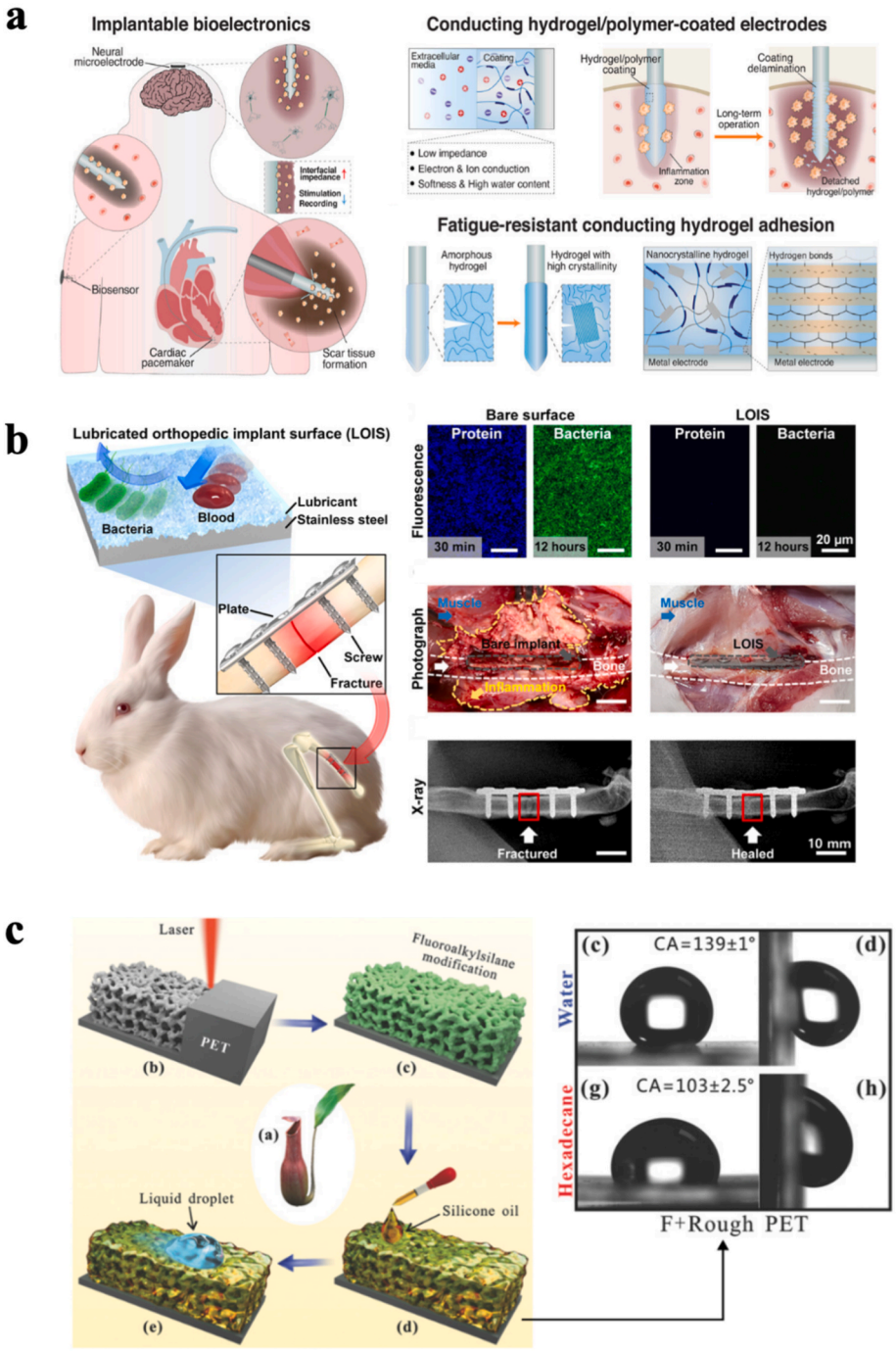

Fig. 8. Nature-inspired coated on an implant for anti-fouling properties. (a) Design of a mechanically-compliant bioelectronic interface with fatigue-resistant hydrogel coating: schematic illustration of implantable bioelectronics for human-electronics interfacing, featuring metallic electrodes coated with conducting polymer hydrogel (PEDOT:PSS). Fatigue-resistant hydrogel (PEDOT:PSS/PVA) coating reduces impedance, enhances conductivity, provides softness, and retains high water content (>70 %), while nanocrystalline domains prevent crack propagation and ensure long-term stability under prolonged stimulation [204]. Copyright 2023 Wiley-VCH. (b) Schematic representation of the LOIS coating with micro/nano-hierarchical structures, evaluated in a rabbit femoral fracture model to confirm its antibiofouling and anti-infection properties. Inspired by the pitcher plant, this biomimetic design incorporates a lubricant layer within the micro/nanostructures, minimizing contact between biosubstances and the surface while ensuring exceptional antibiofouling performance and long-term stability through stable chemical bonding [205]. Copyright 2020 AAAS. (c) Schematic illustration of the fabrication process for a slippery PET surface using femtosecond laser direct writing [207][]. Copyright 2018 Wiely-VCH.

and efficacy through comprehensive testing is essential for securing regulatory approval and enabling the commercialization of novel surface designs. To achieve this, large-scale preclinical and clinical studies, along with systematic meta-analyses of existing data, are necessary to validate these claims and ensure the safe and effective integration of these technologies into clinical practice.

Looking forward, biomimetic surfaces inspired by nature present transformative opportunities for advancing medical device technology. The development of adaptable, multifunctional surfaces has the potential to improve device compatibility, reduce post-implantation

complications, and enhance patient outcomes. Ongoing research and development, coupled with advancements in computational modeling and regulatory alignment, will be essential for the successful clinical adoption of these technologies.

By addressing the challenges of long-term stability and regulatory compliance through robust validation studies, biomimetic surface technologies could eventually deliver safer, more effective, and longer-lasting solutions for medical implants, thereby supporting sustained device functionality and integration within the human body.

CRediT authorship contribution statement

Soo-Hwan Lee: Writing – review & editing, Writing – original draft. **Sungjae Yoo:** Writing – review & editing, Writing – original draft. **Sung Hoon Kim:** Writing – review & editing, Writing – original draft. **Young-Min Kim:** Writing – review & editing, Writing – original draft, Supervision. **Sang Ihn Han:** Writing – review & editing, Writing – original draft, Supervision. **Hyojin Lee:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition.

Ethics approval and content to participate

Not applicable.

Abbreviations

FBR	foreign body reaction
ECM	extracellular matrix
RGD	Arg-Gly-Asp
MIDAS	metal-ion-dependent adhesion site
PMTA	poly([2-methacryloyloxy)ethyl] trimethyllammonium chloride)
SGN	spiral ganglion neurons
DOPA.	dopamine
CuII-DA	copper-dopamine
NO	nitric oxide
PTMAO	trimethylamine N-oxide
UV	ultraviolet
EBL	electron-beam lithography
NIL	nanoimprint lithography
RIE	reactive ion etching
ALD	Atomic layer deposition
CVD	chemical vapor deposition
LbL	Layer-by-layer
PVD	physical vapor deposition
CVD	chemical vapor deposition
Au	gold
Ag	silver
Cu	copper
Pd	palladium
Pt	platinum
SA-PU	sulfanilamide-conjugated polyurethane
γ-PGA	poly-γ-glutamic acid
IAI	implant-associated infection
$Cu_{2-x}S$	Copper sulfide
PEG	polyethylene glycol
PEEK	polyetheretherketone
Cu-TCPP	copper-tetrakis (4-carboxyphenyl) porphyrin
TNZ	tinidazole
OMVs	outer membrane vesicles
SDT/PDT	sonodynamic and photodynamic hybrid therapy
Ta	tantalum
Co-Cr	cobalt-chromium
VBC	4-vinylbenzyl chloride
pVD	2-(dimethylamino)ethylmethacrylate
NPA	nanopillar array
hSPIKE	hydrogel nanospike array
TENG	triboelectric nanogenerator
MPNs	metal-polyphenol networks
TA	tannic acid
Alg-CA	catechol-conjugated alginate
SAFIE	strain-adaptive fiber-interlocked electronic

(*continued on next page*)

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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(*continued*)

PLL	poly-L-lysine
sEVs	small extracellular vesicles
LbL	layer-by-layer
SMCA	shape-morphing cortex-adhesive
PEDOT:PSS	poly(3,4-ethylenedioxythiophene):polystyrene sulfonate
LOIS	Lubricated Orthopedic Implant Surface
APTES	3-aminopropyltriethoxysilane
PEIS	polyethylenimine-quaternized derivative
ELRs	elastin-like recombinamers
AMPs	antimicrobial peptides
IAIs	implant-associated infections
PSer	poly-DL-serine
AI	artificial intelligence

Data availability

Data will be made available on request.

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