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Surface modification of metallic orthopedic implants for anti-pathogenic characteristics

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ABSTRACT

Bacterial infection is one of the main reasons for the long-term failure of orthopedic implants. Despite remarkable progression in antimicrobial drugs, implant-associated infection (IAI) remains difficult to treat, which is resulted from bacterial resistance against antibiotics. As a result, there is an urgent need to develop alternative approaches. The present review highlights surface modification of the orthopedic implants as a promising approach to inhibit bacterial infection. This approach can be classified into two groups: (1) bacteriostatic (anti-adhesive), and (2) bactericidal (contact-killing/release-killing) surfaces. Their combination, which is considered as bacteriostatic-bactericidal bi-functional surface, can provide a more robust approach against dangerous pathogenic species. New approaches and future perspectives in this inspiring field are also provided.

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1. Introduction

Because of the annual population growth, aging population increment, and high functional demands of younger people, requisition for effective and safe materials is significantly increasing [1]. Such materials are commonly used as replacement implants in the knees, hips, ears, and elbows in the human body. Steep growth in respect to knee arthroplasties and hip replacements is reported which is estimated to rise by 673% and 174% up to 2030. In addition, inflammation and trauma in the joint of bones (osteoarthritis), and bones weakening (Osteoporosis) are other factors implicated in the increment of implant surgery [2].

Metallic biomaterials are extensively utilized for manufacturing surgical implants. Titanium and its alloys, 316L stainless steel (316L SS), and cobalt-based (Co-Cr) alloys are the most used metallic biomaterials. In addition, shape memory alloys e.g., magnesium (Mg), NiTi, and tantalum (Ta) are also developing as miscellaneous material implants [3,

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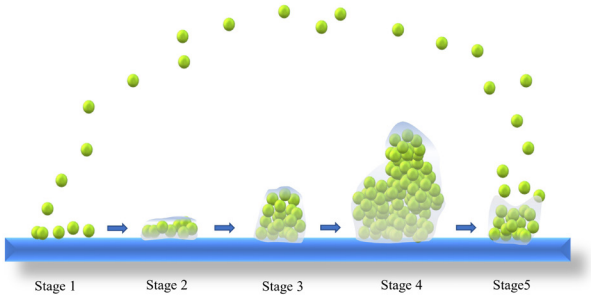

Fig. 1. Schematic of stages of biofilm formation.

4]. Appropriate combinations of acceptable biocompatibility and well mechanical properties including hardness, strength, modulus, plasticity, fatigue life, toughness, etc. make them suitable for long-term implant efficiency in main load-bearing conditions for example in some dental and orthopedic implant applications. These features along with the relative facility of production using well-known and widely accessible methods such as machining, casting, and forging, and also additive manufacturing techniques by sintering or selected laser melting lead to promoting and attention of metal used in the dentistry such as dental implants, restorations, and orthodontic wires and orthopedics such as pins, screws, and plates for artificial joints, artificial spines, fixations, etc. [5, 6].

However, because of IAI, the success of long-term implants could be challenging. It is one of the most prevalent reasons for orthopedic implants failure with catastrophic subsequences for patients including long-term hospitalization, functional incapacitation, revision surgeries, prolonged antibiotic therapy, and even mortality [7, 8]. Adhesion of microorganisms into the surface of implants represents an initial infection step, subsequently causing biofilm formation [9]. Well-known pathogen strains involved in infections are Gram-positive bacteria including *S.* (*Staphylococcus*) *epidermidis, S.* (*Staphylococcus*) *aureus, S.* (*Streptococcus*) *viridans, E.* (*Enterococcus*) *faecalis*, and Gram-negative bacteria including *P.* (*Pseudomonas*) *aeruginosa, E.* (*Escherichia*) *coli, P.* (*Proteus*) *mirabilis, K.* (*Klebsiella*) *pneumonia*, and yeasts (Candida species) [10], among which *P. aeruginosa* and *S. aureus* are accountable of the remarkable number of biofilm-related infections [11]. These infecting organisms are introduced into the implant surface by its contamination during surgery, or the post-operative stage, and or by hematogenous bacteria spreading from presenting infections somewhere else in the host system [12].

Biofilm, as an organized microorganism aggregate within a self-produced extracellular polymeric substance (EPS), attach irreversibly to living or fetish surface [13, 14]. 5-35% volume of biofilm is microorganisms while the remaining volume is constituted by EPS [15]. There are different component types in EPS including protein (>2%), polysaccharides (1-2%), RNA (<1%), DNA molecules (<1%), ions (free and bound), and water (97%) [16]. Bacterial strains become resistant to multiple drugs through this barrier, which prevents them from penetrating immune system cells of the host and antibiotics. Furthermore, reacting antibiotics or biocides with constituents of the biofilm, makes them neutralizing [17, 18]. In other words, biofilms cause to resist phagocytosis, antibiotics, disinfectants, and other ingredients of the innate-adaptive immune system of the host [19].

The concept of surface modification has gained widespread attention over the past few decades on account of their potential to durability extension of engineering and medical devices against destructive factors including wear, corrosion, infection, etc. without any changes in bulk properties [20-22]. Up to date, different modification strategies are being employed to fabricate antibacterial surfaces, which can prevent the colonization of bacteria and implant infection. Based on their functional principle, the antibacterial surfaces can be divided into two main groups: bacteriostatic (passive) and bactericidal (active), which are the subject of the present review [23]. Relying on their intrinsic repulsion property against bacteria, bacteriostatic surfaces are able to prevent or reduce the microorganisms attachment. This can be achieved by altering the surface chemistry (the passive polymer coatings) and topography (superhydrophobic surfaces). Bactericidal coatings can disrupt bacterial membrane integrity by physical interaction through cationic compounds like polymers (contact-killing) or by leaching inorganic or organic compounds from the substrate (release-killing) including antimicrobial peptides, metallic nanoparticles, elemental ions, and antibiotics. The bacteria-free surface can be maintained by such an approach without needing antibiotic therapy and any harmful chemicals [24].

2. Biofilm Formation

irreversible bacterial adhesion threatens the long-term antibacterial surface application, causing biofilms. The formation of biofilms on the surface of biomaterials, as a developmental process, comprises five main stages (Fig. 1): (1) initially reversible bacterial cell attachment to the implant surface, (2) irreversible adhesion, (3) aggregation and cumulation of cells in multiple layers, (4) maturation and differentiation of biofilm, and (5) cell detachment to new cycle initiation of biofilm formation somewhere else [25]. Once implanted, a layer called conditioning film which is mainly composed of proteins covers the surface of the biomaterial. This supports interactions between bacteria and the surface [26]. At first, weak attraction forces e.g., electrostatic, Lifshitz Van der Waals, hydrophobic forces mediate the surface protein-bacteria interactions and subsequently specific chemical interactions including adhesive proteins of bacteria and production of EPS strengthen bacteria adhesion to the surface [27, 28]. After that, bacteria cell duplication and division lead to the formation of micro-colonies, as the basic organized biofilm unit. Then, biofilm is matured by bacteria accumulation and intercellular adhesion in multiple bacterial layers. Finally, because of nutrient depletion, the detachment of microorganisms from the biofilm occurs, entering into the bloodstream and spreading infections [29].

3. Bacteriostatic Surfaces

Characteristics of implants surface such as surface energy, surface roughness and chemistry, surface potential, conductivity, and hydrophilicity play an incisive role in the initial adhesion of bacteria to implants and thereby the formation of biofilm. These characteristics can affect the conformation and/ or amount of adsorbed proteins, therefore, affecting subsequent bacterial adhesion and biofilm formation. Modification of the surface is an economic and simple way to change these physicochemical properties for creating favorable anti-adhesion characteristics without any bulk properties changes. This passive strategy, as a bacteriostatic approach, depends on specific surface chemistry and/or topography [30, 31].

3.1. Passive Polymer Coating

The biopassive polymer coating provides minimal adsorption of proteins on the implant surface and therefore hindering bacterial adhesion. A broad range of polymers comprising poly(ethylene glycol) (PEG), Poly(2-oxazoline)s (POxs), and Poly-zwitterionic polymers have been subjected to many investigations as the biopassive surfaces [32-34].

PEG and its derivatives are the desirable candidates to create anti-

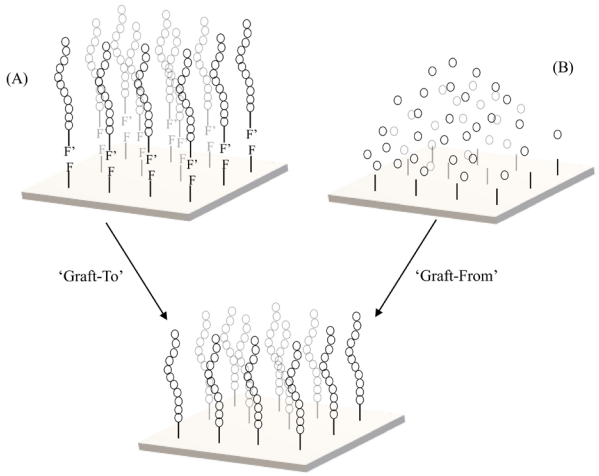

Fig. 2. Schematic of polymer grafting through (a) the 'graft-to' approach, in which the reaction between functional groups (F, F') leads to the surface immobilizing of pre-formed polymers, (b) the 'graft-from' approach in which graft polymers are covalently immobilized by utilizing chain transfer agents or surface-immobilized initiators in a monomer solution.

fouling interfaces, resisting non-specific protein adsorption as well as cell and bacterial adhesion. They have been considered as the "gold standard" of antifouling polymers [35]. Polymer brushes and self-assembled monolayers (SAMs) are the common forms of these coatings. Polymer brushes provide greater chemical and mechanical robustness over SAMs, leading to greater long-term stability [36].

Physisorption and covalent attachment are used to make polymer brushes [37]. Kingshott et al. [38] reported a bacterial adhesion reduction in covalently bonded PEG coatings leastwise two orders magnitude greater than PEG layer physisorbed to the substrate, because of its high coverage and stability. "Graft-to" and "graft-from" are the commonly used approaches to accomplish covalent attachment (Fig. 2). The Graft-to approach is directly grafting of pliable, hydrophilic end-functionalized polymers to a surface. These coatings require high graft densities to be effective. Because of the steric obstacles of the adjacent chains, this is not easy to attain with the "graft-to" approach. In "graft-from", an in-situ surface-initiated polymerization [e.g., atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT)] forms pliable, hydrophilic polymer chains. This approach provides improved graft density thereby resistance against proteins [39].

A biologically inspired approach to PEG attachment to different substrates has been also developed by using muscle adhesive protein components i.e., 3,4-dihydroxyphenylalanine (DOPA) via catechol group [40]. In this regard, Dalsin et al. [41] reported that end-functionalized (peptides containing three DOPA residues) monomethoxy-terminated PEG (mPEG-DOPA) attached to the titanium oxide (TiO_2) surface has a high ability to resist proteins upon exposure to human serum. A charge-transfer complex among Ti-OH and DOPA groups is reported to form, tethering the polymer onto the surface of TiO_2. Also, PEG side chains can be introduced into the polycationic backbone (i.e. poly(L-lysine) (PLL)) to anchor PEG to the surfaces of metal oxides via amine groups, forming comb-like copolymers (PLL-g-PEG) [42]. In addition, functionalization of the lysine side chain with Arg-Asp-Gly (RGD) integrin ligand can be done to give the specific binding ability of the surface to the host cells [43]. To enhance the stability of physisorbed PLL-g-PEG coatings, functionalization of a fraction of the amine-terminated side chains of the lysine can be done with catechol groups. In this regard, Saxer et al. [44] grafted a catechol derivative, 3,4-dihydroxyphenylacetic acid (DHPAA), with different fractions to the PLL backbone, forming PLL-g-(DHPAA; PEG) copolymers and examined polymeric layer chemical stability upon exposure to high ionic salt solutions. Unlike the control PLL-g-PEG copolymer, PLL-g-(DHPAA; PEG) remained non-fouling due to stable catechol-substrate anchorage.

It is worthy to note that the high mobility of PEG chains, steric hindrance, and great exclusion volume effect of the highly hydrated layer make it non-fouling [37]. However, several variables including chain length, grafting density, and kind of branching architecture determine the effectiveness of PEG [45, 46].

Even though PEG is frequently used to provide protein-resistant surfaces, it is exposed to oxidative breakdown and chain cleavage, leading to loss of surface hydrophilicity, and resistance against non-specific adsorption that restrict its long-term usage [47].

Poly(2-oxazoline)s (POxs) including poly(2-ethyl-2-oxazoline) and poly(2-methyl-2-oxazoline) are considered as the prominent alternatives to PEG [48]. They offer extended period antifouling character and less oxidative degradation in oxidative and biological media, relative to PEG. As a consequence, they have gained considerable attention as the non-fouling surface coatings [49]. POxs with the optimized grafting density have close protein repellency to PEG and different techniques are used to anchor them to the surface including "graft-from," "graft-to," and PLL-g-POx copolymers [48].

Further, Zwitterionic polymers have recently become promising PEG alternatives. They are a subset of materials with equal anions and cations alongside their polymer chains. These polymers comprise negative and positive charged groups embedded into their structure, which make them greatly hydrophilic non-fouling compounds. based on anions, zwitterionic polymers can be categorized into phosphorylcholine (PC), sulfobetaine (SB), and carboxy betaine (CB) [24]. Similar to PEG, their antifouling properties are firmly correlated with the hydrated layer formed on these polymers, acting as the physical obstacle for proteins and bacteria adhesion. zwitterionic polymers show extremely low adsorption of proteins, because of their net charge neutrality. Further, the hydrophilicity of these polymers is more than PEG owning to an intense interaction with molecules of water through ionic solvation rather than hydrogen bonding utilized by PEG, enhancing antifouling properties of zwitterionic materials [50].

3.2. Surface Morphology Modification

Another approach to prevent the initial bacterial attachment is to utilize superhydrophobic surfaces with a contact angle > 150° and roll-off angle <10° (the minimum surface inclining angle at which droplets of liquids start rolling off) for water. These are at odds with superhydrophilic surfaces, displaying low contact angles typically <10°. Because of their low surface energies which decrease contaminants and water adhesion and thereby make them simple to clean, superhydrophobic surfaces have been subjected to investigations for antifouling properties [51].

The basic rule to make superhydrophobic surfaces is creating roughness over a surface through different techniques including template deposition, solution immersion, electrodeposition, spray coating, chemical etching, etc. followed by functionalization via material with low surface energy [52].

Non-wettability of the superhydrophobic surfaces is the basic principle behind their usage for bacterial biofilm reduction which does not favor the attachment of planktonic bacteria [51, 53, 54]. For superhydrophobic surfaces, synergistic actions of surface energy and roughness improve the property of the surface. Minimal contact between the implant surface and the bacteria is feasible to attain with efficient roughness. Alongside such benefits, the cells of bacteria respond to the topography of the surface (particularly with micron-sized roughness) which changes their morphology leading to strong attachment over the surface [55]. The surface energy significance of the substrate has been pointed out, influencing the adhesion dynamics of the bacteria i.e., lower surface en-

ergy leads to the reduction in bacterial adhesion [56]. Hence, besides roughness, the low energy of the surface has equal importance. In other words, appropriate roughness and low energy of the surface lead to the contact area reduction and the adhesion restriction, respectively. In this regard, Tang et al. [57] carried out titanium substrate modification with TiO_2 nanotubes and subsequent functionalization with 1H, 1H, 2H, 2H-perfluorooctyl-triethoxysilane (TiS) to obtain a superhydrophobic surface. Super-hydrophobicity was observed to effectively decrease the adhesion of the bacteria over titanium surface with nanotube and titanium surface-functionalized with TiS. Moazzam et al. [58] modified an aluminum surface with micro/nanostructure and silanized to achieve super-hydrophobicity, which not only could provide an ability to control bacterial adhesion, protein adsorption, and biocompatibility but also could obviate the issue of Al-alloys long-term toxicity [59].

4. Bactericidal Surfaces

Even though the adhesion of bacteria can be significantly reduced by micro-structuring or surface coating, it is not easy to entirely remove adhesion, and attachment of some bacteria may still occur to the implant surface. This can provide biofilm development on the surface of the implant, which is troublous to treat. Hence, it is important to employ a second defense line dealing with bacteria that overcome the antifouling function of the surface treatment. Contact killing is an approach to eliminate adhered pathogens entirely. This kind of anti-infection approach is generally comprised of bactericidal agent immobilization on the implant surface, therefore making a functional surface with the bactericidal ability [60].

4.1. Active Polymer Coating

The cells of microbes commonly contain a net negative charge because of the presence of negatively charged phospholipids at the exterior Gram-negative bacteria's membrane and teichoic acid membrane protein in Gram-positive bacteria. Hence, cationic polymers can provide effective adsorption at the surface of the bacterial cell. such cationic polymers can simply penetrate through the membrane of the cell, as they are sufficiently amphiphilic. This leads to cell disruption, causing cytoplasmic constituent leakage, which eventually induces the death of the cell. Therefore, cationic polymers have been employed to design greatly vigorous antimicrobial surfaces, which can offer the killing of bacteria just via contact. The suppositions of these polymers' action in bacteria-killing have been corroborated by many pieces of research using atomic force microscopy (AFM), two colors fluorescence assays, transmission electron microscopy (TEM), monitoring the loss of constituents of the bacterial cell, and dye leakage from liposomes which imitate the membrane of bacterial cell [61]. Cationic polymers most likely damage the wall of the cell membrane via lysis, inducing the dissemination of cellular constituents in the solution. The antimicrobial efficacy of the cationic polymers is directly commensurate with the number of cationic groups, constitutive alkyl chain length, and hydrophobicity [62]. Cationic polymers with antimicrobial functions are summarized in Table 1.

4.2. Antimicrobial Peptides

Antimicrobial peptides (AMPs), immune effector molecules of plants, animals, and microorganisms, have gained considerable attention as the agents solving the problems related to IAI. In other words, they present antimicrobial activity against antibiotic-resistant bacteria which reside within the biofilms [72]. AMPs are mainly cationic, amphipathic peptides, displaying antimicrobial activity against fungi, bacteria, and (enveloped) viruses. Interaction of AMPs with the specific component of the cell envelope of the bacteria results in destabilization, disruption, and/or depolarization of the plasma membrane of the bacteria, causing to death of bacterial cells within minutes [73]. In this regard, Kazemzadeh-Narbat et al. [74] coated the titanium surface with calcium phosphate loaded with Tet213 (KRWWKWWRRC), a cationic antimicrobial peptide, (CaP-AMP). They reported the ability of CaP-AMP coating to kill both *P. aeruginosa* and *S. aureus* bacteria within 30 min *in-vitro*. A parotid secretory protein-derived AMP, called GL13K, has been demonstrated to have both bacteriostatic and bactericidal capacity [30]. GL13K peptide coating is bactericidal *in-vitro*, inhibiting the growth of biofilm for peri-implantitis' pathogens, for instance, *P. aeruginosa*, *P. gingivalis*, and *Strep. gordonii* under static growth conditions [75, 76]. In addition, antimicrobial activity of AMP surfaces has been reported against *E. coli* and *S. epidermidis* under static growth conditions [77] and *Strep. gordonii* under dynamic growth conditions [78]. A summary on AMPs are presented in Table 2.

Because of the non-specific and rapid action mechanisms, the risk of development of resistance is typically considered to be low. However, the resistance of bacteria to AMPs can happen and several resistance mechanisms have been reported which include envelope structure alterations of cell and membrane envelope enhancing positive charge, efflux pumps upregulation, and peptide proteolytic degradation [88]. For example, it has been reported that resistance to the human cathelicidin LL-37 includes the peptide degradation via bacterial proteolytic enzymes, efflux pumps upregulation, and also down-regulation of LL-37 induced by bacteria [89]. In low concentrations of magnesium or calcium ions, like in blood plasma, the activation of pmr (polymyxin resistance) op-

Table 1.
Cationic polymers with antimicrobial function.

Polymer	Action Mechanism	Affected Bacteria	Ref
Quaternary Ammonium Compounds (QAC)	denaturing structural enzymes and proteins through the electrostatic interaction between the negatively charged membrane of bacteria and positively charged QAC and afterward hydrophobic QAC tail integration into the hydrophobic membrane core of bacteria.	*MRSA*	[63, 64]
Chitosan	pH-dependent antimicrobial activity. hydrophobic interaction and chelation effects at pH>pKa and electrostatic interaction between the cell wall of bacteria and protonated amino groups at pH< pKa results in antibacterial activity.	*E.coli, S. aureus*	[65-67]
Poly- ε -lysine	Destruction of the bacterial membrane structure and acceleration of the death of bacteria through surface potential interference and oxidative stress induction.	*E. coli, MRSA*	[68, 69]
N -halamines	cell inactivation or cell inhibition through targeting amino or thiol groups of proteins by oxidative halogen (Br^+ or Cl^+), upon direct contact.	*E. coli, S. aureus*	[61, 70]
Polyethylenimine (Branched)	Rupture of bacterial cell membrane via electrostatic interaction between the negatively charged membrane of bacteria and positively charged polyethyleneimine	*P. aeruginosa, MRSA*	[67, 71]

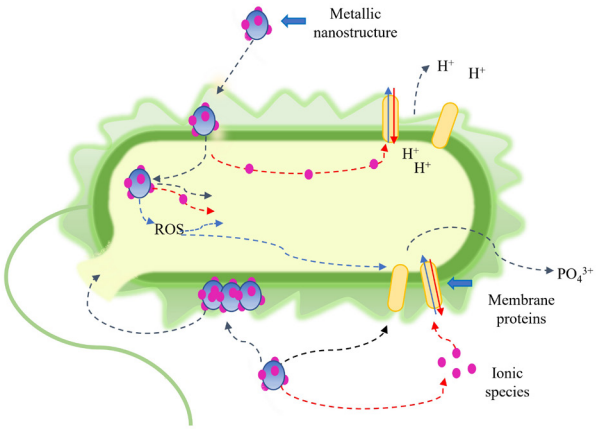

Fig. 3. Schematic of antibacterial mechanisms of mNPs.

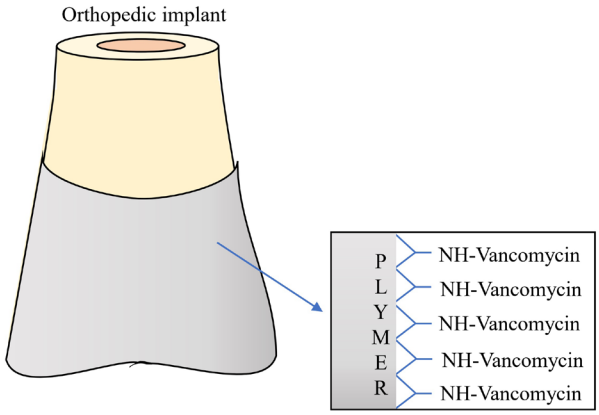

Fig. 4. Schematic of Vancomycin covalently linked to the polymer surface.

eron occurs by *P. aeruginosa,* medicating N-arabinose addition to its lipopolysaccharide. This makes the exterior bacterial cell's surface more positively charged, and consequently repels the cationic AMPs [89]. Therefore, bacterial resistance to AMPs is feasible for several species of bacteria, but it has not been examined such resistance development to novel synthetic AMPs.

AMPs show not only direct antimicrobial activity but also immunomodulatory activities. For instance, they can hinder the excessive pro-inflammatory responses resulting from endotoxins of bacteria such as lipoteichoic acid and lipoteichoic acid of Gram-positive bacteria and lipopolysaccharide of Gram-negative bacteria [90].

Wound healing, osteogenic, and angiogenesis activity are the other desired characteristics of AMPs. In-vivo study of trabecular bone growth has found osteoconductive properties of cylindrical Ti implants coated with HHC36, an antimicrobial peptide [82]. Similarly, pro-osteogenic and anti-biofilm activities have been displayed by fusion peptide P15-CSP [91]. Further, in NOD/SCID mice, acceleration of bone repair and rat calvarial bone defect model, promotion of bone regeneration has been provided by LL-37 [92, 93]. However, high manufacturing cost, uncontrolled toxicity, degradation via the host proteases, and cytotoxic effects on eukaryotic cells have limited practical applications of AMPs [94].

Table 2.
Overview of AMP associated coatings

AMP	Coating system	Substrate	Affected Bacteria	Ref
HHC-36	TiO2 nanotubes	Ti	S. aureus	[79]
	TiO2 nanotubes, CaP, POPC	Ti	S. aureus, P. aeruginosa	[80]
Tet-213	poly(DMA-co-APMA) brush	Ti	P. aeruginosa	[81]
	CaP	Ti	S. aureus, P. aeruginosa	[82]
Tet-213, Tet-20, Tet-21, Tet-26, 010cys, HH2, MXX226	PDMA brush	Ti	S. aureus, P. aeruginosa	[83]
LL-37	-	Ti	P. aeruginosa	[84]
PSI-10	HA	AZ91	S. aureus	[85]
Nisin	-	Stainless steel	E. coli, Bacillus subtilis	[86]
magainin I	-	Stainless steel	Listeria ivanovii	[87]

4.3. Metallic Nanoparticles

The coatings and/or surfaces incorporated with metallic nanoparticles (mNPs), as the modern generation of surface modification, have been subjected to extensive *in-vitro* and *in-vivo* preclinical studies [95, 96]. Functionalization of surfaces via loading or charging with some type of compounds or mNPs offers numerous benefits over common surfaces. These systems have shown desired outcomes, including inhibition of bacterial adhesion and biofilm formation, betterment of adhesion and osteogenic expression, and even anti-inflammatory efficacy [97]. Many pieces of research have focused on the antibacterial application of mNPs, generated from silver, gold, copper, zinc, and some other metals [95, 98, 99].

In general, the action of the antibiotics involves the inhibition of survival factors, or evolution of the bacterial cell, which favor acquired resistance mechanisms with effect reduction over time. It should be noted that resistance development against metals is more intricate for the cells of bacteria. They also have antibacterial ability against a wide spectrum of gram-negative and gram-positive bacteria. As result, the usage of systems releasing mNPs is in high demand on the systemic antibiotics reduction for topical surgery [100].

The antibacterial mechanisms of mNPs might differ depending on their type [24]. The accepted mechanisms to damage the cells of the bacteria include oxidative stress via reactive oxygen species (ROS) generation, free metal ions release which acts through the intra- and extra-cellular pathways, and disruption of the membrane via their physical structures (Fig. 3) [97].

covalently immobilization or coating of mNPs onto the implant surface provides antibacterial functioning to the surface [24]. For example, Gao et al. [101] employed TiAg magnetron sputtering and anodization to prepare Ag_2O nanoparticle embedded TiO_2 nanotube (NT) arrays. They reported the ability of NT-Ag_2O arrays to kill *S. aureus* and E. coil even after 28 days immersion, showing long-term antibacterial capacity. Similarly, Hengel et al. [102] used plasma electrochemical oxidation to fabricate zinc and silver nanoparticles embedded TiO_2 layer on the porous titanium implant surface. Releasing of zinc and silver ions was reported for up to 28 days, showing well bactericidal activity to methicillin-resistant S. aureus (MRSA). Further, producing ROS by bio-functionalized implants facilitated the ability of bacterial contact killing. In addition, their loading into the hydrogel and subsequently coating onto the implant surface offer an antibacterial action. In this regard, Xu et al. [103] loaded Ag NPs into poly(hydroxyethyl methacrylate) hydrogel with interconnected, spherical pores. good antibacterial properties were shown against both Gram-negative bacteria *(E. coli)* and Gram-positive

bacteria (*S. aureus*) *in-vitro*. It was also greatly effective at bacterial cell growth inhibition. The main mNPs used in the bactericidal system for implants are presented in Table 3.

Interaction between nanomaterials and biological systems is significantly affected by their surface charge, shape, aggregation status, and size. The great importance of these parameters has been reported for nano-silver (nAg) to its antibacterial activity. A higher surface-to-volume ratio is possessed by nAg with the smaller size, which facilitates Ag ion release by providing more Ag atoms exposed to the biological solution. Further, entrance to bacteria can be simplified by small nAg, and ROS generation can be promoted because of its high surface energy, which causes stronger oxidative stress in the cells of bacteria [104]. however, greater cytotoxicity against host cells has been shown by the smaller ones. [24].

4.4. Ion Implantation

Because of broad-spectrum bactericidal activity of elemental ions such as chlorine (Cl), calcium (Ca), fluorine (F), iodine (I), zinc (Zn), selenium (Se) cerium (Ce), and copper (Cu) against both Gram-negative and Gram-positive bacteria, they are mostly considered to fabricate the antibacterial coatings. The ions' bactericidal activity is dependent on their gradual release from the implant surface into the surrounding host tissue. hydroxylation into greatly reactive species including hydrogen peroxide (H_2O_2), hydrochloric acid (HCl), superoxide (O^{2-}), hypochlorous acid (HOCl) is one of the bactericidal mechanisms of implanted ions, which leads to bacterial cell membranes oxidation, causing enhanced cell permeability and eventually death of the cells. They can also cause to prevent bacterial metabolism [116, 117].

In the field of orthopedic implants, stimulating bone integration and bacterial infection prevention can be simultaneously achieved by the incorporation of antibacterial metallic ions into bioactive materials such as hydroxyapatite (HA). In this regard, several antibacterial HA coatings including Cu-carbonated HA [118, 119], Ag-HA [120], Ag/Sr-HA [121], Cu/Zn-HA [118], Sr/Cu-HA [122], have been developed. For instance, Hidalgo-Robatto et al. [123] produced HA coatings doped with Zn and Cu on the implant surfaces via pulsed laser deposition (PLD) for simultaneous osseointegration promotion and biofilm formation inhabitation. doping of Zn and Cu provided antibacterial features to the coatings, leading to a notable reduction in *S. aureus* and *E. coli* biofilms [124].

Table 3.
mNPs-containing composite coating used for IAI prevention.

mNP	Coating System	Substrate	Affected bacteria	Ref
Ag	CaP, TiO_2 nanotubes	Ti	S. aureus	[105]
	polyacrylate-based hydrogel	Ti	S.aureus, E. coli P.aeruginosa	[106]
	CaP	Ti-6Al-4V	S. aureus	[105]
	poly(dl-lactic-co-glycolic acid)	stainless steel alloy(SNPSA)	MRSA	[107]
ZnO	Chitosan/TiO_2 layer	Ti	E. coli	[108]
	TiO_2 nanotubes	Ti	S. aureus	[109]
	bioactive glass/alginate	316L stainless steel	E. coli	[110]
Cu	HA	Ti	S. aureus, E. coli	[98]
	Poly(ethylene glycol diacrylate) hydrogel	316L stainless steel	S. aureus, E. coli	[111]
Au	Chitosan	316L stainless steel	S. aureus, E. coli	[112]
	TiO_2 nanotubes	Ti	S. aureus, E. coli	[113]
	Chitosan/bovine serum albumin	Ti-6Al-4V	E. coli, Bacillus subtilis	[114]
	Chitosan	NiTi	S. aureus	[115]

4.5. Antibiotic-Loaded Coatings

Infections have been often treated with antibiotics. However, as described above, the unsuitable usage of antibiotics has resulted in the development of many kinds of antibiotic-resistant bacteria, mainly MRSA. Recently, multiantibiotic-resistant superbugs have also developed, which bring high challenges for controlling clinical implant infection. Contrary to the conventional infection management via systemic antibiotics, the effective concentration of antibiotics can be achieved by antibiotic-loaded coatings, providing local drug delivery. The risk of antibiotic resistance can be also decreased by the local antibiotic application. Mixing and co-deposition the antibiotic molecules with the polymer matrix is the conventional manner to make the antibiotic-loaded coatings [125, 126].

A wide range of antibiotics including levofloxacin, gentamicin, vancomycin, etc. has been used to gain surface antibacterial properties (Table 4). In addition, phytochemicals such as ferulic acid and curcumin are recent of interest, because they do not cause the resistance of bacteria over their synthetic counterparts [127, 128]. Further, they can combine with bioactive materials to increase the biological coating's performance. This is caused by the synergistic interaction of the released bioactive ions and phytochemical compounds at the implant site [129].

However, controlled release of the antibiotics is difficult to be achieved by the conventional single-layer antibiotic-loaded coatings. In these systems, a large part of the loaded antibiotics is released after a very short period [125], since inter-molecular bonding between the components of the coatings and the molecules of the antibiotics is weak [130]. This burst release provides the development of opportunistic pathogens by limitation of bactericidal time and serious tissue toxicity may be induced by releasing the high antibiotic concentrations locally [131]. To obviate this problem, the chemical conjugation of small-molecule anti-

Table 4.
Bactericidal coatings containing antibiotic drugs.

Antibacterial Agent	Coating System	Substrate	Affected bacteria	Ref
Vancomycin	calcium phosphate	Ti	S. aureus	[137]
	TiO_2 nanotubes	Ti	S. aureus	[138]
	Chitosan/BG	Ti	MRSA	[130]
	-	Ti alloy	S. epidermidis	[139]
Gentamicin	poly(d,l-lactide) (PDLLA)	Ti	S. aureus	[140]
	TiO_2 nanotubes	Ti	S. aureus	[141]
	Chitosan/gelatin/silica NP	316L stainless steel	S. aureus, E. coli	[142]
levofloxacin	Graphene	Ti	S. aureus, E. coli	[143]
Fusidic acid	Chitosan/BG	316L stainless steel	S. aureus, E. coli	[128]
Rifampicin	Mg silicate	Ti	S. aureus	[144]
Fusidic acid and Rifampicin	PLGA nanofibers	Ti	MRSA, S. epidermidis	[145]

biotics to the surface through linkage bonding can be used (Fig. 4) [132]. Antibiotic interruption into the delivery carrier, including mesoporous silica-based nanoparticles [133], halloysite nanotubes [134], magnetic nanoparticles [135], or titania nanotubes [136], and their co-deposition with the matrix of material is another approach, extending the duration of the antibiotic release.

5. Bacteriostatic-Bactericidal Bi-Functional Surface

The incorporation of the antimicrobial agent into an antifouling background has been provided the improvement of antibacterial properties of implant surfaces by the synergistic effect of active and passive approaches. For instance, Peyre et al. [146] reported both bactericidal and protein-repellent surfaces can be achieved by the grafting of magainin I, the antimicrobial peptide, to the surface of TiO_2, through a PEG cross-linker. Wang et al. [57] used in situ crystallization technique to coat the Ti alloy surface with thin zeolite film under hydrothermal conditions. To possess antibacterial properties, the Incorporation of a small amount of Ag ions into the zeolite film was done via the ion-exchange process. The antibacterial studies showed Ag-incorporated zeolite coatings significantly inhibit the proliferation of bacteria (MRSA) both on the Ti surface and in the medium of the culture surrounding the Ti material. Further, the additional antifouling feature was provided by the superhydrophilic character of zeolite coating.

To use bi-functional surfaces it must be ensured that biopassive background does not prevent contact between the bacteria and antimicrobial agents. In addition, polymers' biopassive properties can be reduced by antimicrobial agent incorporation. Switchable antibacterial surface advancement is one of the exciting solutions to overcome this issue [147]. The basic of these surfaces is their capability in function switching, consequently being considered within a multi-function approach. This can promote the bacteria-releasing and bacteria-killing ability of the surface [24]. In this regard, Cheng et al. [148] created antifouling and bactericidal switchable surfaces through the conversion of antimicrobial cationic poly(N,N-dimethyl-N-(ethoxycarbonylmethyl)-N-[20-(methacryloyloxy)ethyl] ammoniumbromide) (pCBMA-1 C2) to non-fouling zwitterionic pCBMA-1 by pH change. More than 99.9% of E. coli was effectively killed by cationic pCBMA-1 C2 in 1h. Then, by the pH change, the cells of dead bacteria (98%) were released after hydrolyzing of cationic derivative to the zwitterionic polymer.

6. Candidates in Orthopedic Surgery

Silver has been employed in the orthopedics field for over a decade. MUTARS® is one of the most versatile systems for bone replacement which is available in a silver-coated version. In this system, a layer of gold is applied and elementary silver is galvanically deposited onto the implant surface [149]. However, the application of such coatings has been restricted in patients with high postoperative infection risk because of their toxicity issues. A lower profile risk can be provided by low-content silver coating such as Agluna, in which Ag ions stitch into the anodized titanium surface by ion-exchange reaction [150]. Another candidate for antibacterial application in orthopedics is iodine-supported implants, which have been numerously investigated in clinical trials. Gradual leaching of iodine over time makes these coatings favorable for long-term applications [151, 152]. Despite desired antibacterial features provided by surface modifica-tion approaches, there is only one randomized-controlled study that was conducted in five European orthopedic centers. They investigated the efficacy of antibiotic-loaded (ciprofloxacin, vancomycin, meropenem,gentamicin, rifampicin, and daptomycin) hydrogels in the prevention of implant infection over control implants and reported a significant reduc-tion in infection by this system [153]. This is indubitably insufficient to develop such approaches for practical applications and more clinical evidence is needed.

7. New Approaches and Future Perspective

Since none of these antibacterial coatings and surface modification techniques can completely meet clinical requirements, multifunctional and smart coatings are in great notice. There is no distinct formula for these coatings, and these coatings are mainly designed based on our requirements. One model of multifunctional coatings is based on three parts: 1) An anti-adhesive coating to inhibit bacterial adhesion, 2) A bactericidal coating to kill adhered bacteria, and 3) RGD sequences to enhance cell adhesion and osseointegration [154]. Table 5 provides some recent developments in multifunctional and smart coatings and their result. Today nanocontainers conjoined to sensors are in development. The sensor can recognize a small number of bacteria. After recognition, sig-nals are sent to nanocontainers. The shell of nanocontainers is made of stimuli-responsive materials that respond to signals coming from sen-sors and start to release biomolecules and therapeutic agents entrapped in them. Multifunctional coatings can also enhance the physical, chem-ical, and mechanical properties of implants [161]. These coatings are more operational than any single method, hence the future of antibacte-rial coatings is in this path.

Table 5.
Recent developments in multifunctional and smart coatings

Substrates	Biofunctional Elements	Observations	Ref
Ti	PEG + RGD	Reduced S. aureus adhesion; Cell adhesion not studied	[42]
Ti6Al4V-dopamine	Dextran + BMP-2	Less S. aureus and S. epidermidis; increased osteoblast response	[155]
Ti-dopamine	CM-CH + VEGF	Reduced S. aureus adhesion; increased osteoblast response	[156]
Ti6Al4V-dopamine	CM-CH + BMP-2	Reduced S. aureus and S. epidermidis adhesion; increased osteoblast and mesenchymal stem cell response	[157]
Ti	TNT + Ag2O NPs	Reduced S. aureus and E. coli; osteoblast-like response not influenced compared to TNTs	[158]
Ti	BMP-2 + vancomycin	Reduced S. epidermidis growth; increased bone marrow stromal cell response	[159]
Ti	EGF + magainin II	Reduced S. aureus and E. coli adhesion; increased fibroblast adhesion	[160]

8. Conclusion

The usage of orthopedic implants is in high demand for prosperous treatment of musculoskeletal problems. Nevertheless, infection is one of the main challenges over the success of implantation procedure, resulting from bacterial adhesion to the implant surface and presenting inevitable clinical, social and economic burden. Hence, many efforts have been made to fabricate the implants with antibacterial property. The ideal approach is to modify the implant surface via altering the surface chemistry or topography which has been highlighted in this review. This approach has been divided into bacteriostatic and bactericidal surfaces, depending on their functional principle against bacteria, which is summarized in Table 6. The combination of these strategies can improve the antibacterial properties of implant surfaces by their synergistic effect.

Table 6.
Surface modification strategies required to prevent bacterial infection.

Approach	Function	Subcategory	Remark	Limitation
Bacteriostatic surface	Anti-adhesive	Topographic modification, Passive polymers coatings	Prevention of bacterial adhesion via their low surface energy, electrostatic repulsion, and steric exclusion repulsion	Attachment of some bacteria
Bactericidal surface	Contact active	Active polymer coatings	Rupture of bacterial cell membrane via electrostatic interaction	Accumulation of dead bacteria
	Biocide release	antimicrobial peptides, metallic nanoparticles, ion implantation, antibiotic-loaded coatings	Death of bacteria via release of antibacterial agent	

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