Phenolic Compounds-Based Functional Coatings: Versatile Surface Chemistry and Biomedical Applications

Van Cuong Mai, Di Li and Hongwei Duan*

School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University, 70 Nanyang Drive, 637457, Singapore.

Corresponding author: hduan@ntu.edu.sg

Abstract: Phenolic compounds-based functional coatings that allow for flexible modulation of chemical and surface properties have found widespread uses in a diverse range of biomedical applications from antibiofouling and antioxidation to bioimaging, therapeutics and controlled drug delivery. It is imperative to understand the formation mechanism of phenolic coatings to fully meet the needs of their emerging applications in controlling the surface properties of biomaterials and medical devices. In this Perspective, we highlight the versatile chemical and self-assembly approaches to generate the phenolic coatings with tailored surface properties and reactivities, and also discuss how the surface properties and chemical reactivities impart functional materials for translational research.

1. Introduction

Phenolic compounds are a diverse class of naturally occurring substances ubiquitously present in organisms. Dopamine (DA), caffeic acid (CA), gallic acid (GA), pyrogallol (PG), tannic acid (TA), and green tea polyphenols including epigallo catechin gallate (EGCG) are the representative members of this huge family. Their distinctive physiochemical properties have stimulated intense research interest in these molecules found in fungus, bacteria, plants, and mammals. Wait et. al identified phenolic-containing proteins (also known as mussel adhesive protein) in the adhesive pads of sea mussels in 1981.[1] The discovery of adhesive mechanism of mussels subsequently promoted the development of biomimetic synthetic polymers and peptides that contain catecholic groups. Messersmith and co-workers pioneered self-polymerization of dopamine into polydopamine (PDA), which mimics the mussel adhesive protein to exhibit universal adhesion with nearly all known solid substrates.[2] The same group later also reported multifunctional, colorless, and adherent films of polyphenols on a variety of metal, ceramic and polymer.[3] More recently, Caruso and co-workers reported that TA, a plant polyphenol, and Fe^{3+} were able to assemble via coordination to create a simple and conformal coating for a variety of solid substrates and colloidal particles.[4] These pioneering findings stimulated intense research and development in phenolic-based coatings for a wide range of practical applications by taking advantage of their universal adhesion on functional substrates.

Polyphenol-based functional coatings have recently gained tremendous attentions in biomedical engineering, in which the conformal coatings became general platforms to tailor surface properties of biomaterials and their interfaces with biological systems. The unique physiochemical activity of catechol and gallol moieties of polyphenols leads to strong interactions with manifolds of materials via hydrogen bonding, π-π interactions, hydrophobic interactions, metal coordination, covalent bonding, and electrostatic interactions, which account for the robust adhesion of polyphenols.[5] The robust coatings also offer new possibilities of introducing surface functionalities for controlled molecular/cellular interaction and chemical catalysis by subsequent covalent and/or non-covalent modifications, forming the fundamental basis of their diagnostic and therapeutic applications. To present a comprehensive image of phenolic-based coatings, this work aims to highlight recent advancements, starting with their unique surface properties and growth mechanism prior to discussing their specialized uses in functional modifications of medical devices covering antimicrobials, antibiofouling, therapeutics, controlled delivery, and diagnostics. This evaluation is of value for those working in functional coatings, bio-inspired material synthesis, supramolecular chemistry, and

translational medicine for rational design of phenolic-based coatings with specific structural attributes.

2. The Mechanism of Coating Formation

2.1. Oxidative Polymerization

Mussel-inspired surface modification has been employed widely to construct multifunctional structures due to its simplicity, robustness, versatility and multifunctionality. Taking PDA as an example, DA can undergo self-polymerization overnight under an aerial oxidation condition (*i.e.*, pH=8-8.5) to form a layer of PDA on diverse substrates via both covalent interaction and non-covalent assembly (Figure 1A).[6] The robust adhesion of PDA resulted from a high content of catechol and primary/secondary amine moieties, which mimic the presence of 3,4-dihydroxy-L-phenylalanine, lysine and histidine residues in the wet adhesive biomolecule-foot proteins from mussels. However, the growth rate of PDA in this approach is relatively low at 1.2-2.1 nm/h, leading to a coating thickness of 45 ± 5 nm after 24h. Of note, this conventional method employs dissolved oxygen as the catalyst. Exogeneous addition of oxygen was shown to accelerate PDA coating rate to 8 nm/h.[7] Increasing dopamine concentration from 2 mg/ml to 8 mg/ml in aerial oxidation also accelerated the coating rate to 4 nm/h with the maximum coating thickness is 80 nm.[8] The combination of metal ions, such as Cu^{2+} or Fe^{3+}, and hydrogen peroxide (H_2O_2) can greatly promote the self-polymerization due to the production of reactive oxygen species (ROS), strong oxidants, released during the activation of Fenton-like reactions.[9,10] ROS produced under UV irradiation has also shown a supportive acceleration of PDA coating formation. For example, Levkin et al. successfully deposited various dopamine and plant-based polyphenols in both polar and nonpolar surfaces using UV irradiation.[11,12] It was found that the control of oxygen, ROS and pH was crucial for a fine layer of PDA and plant polyphenols within 2h, which was much quicker than traditional oxidation of those monomers in mild alkaline condition with only the presentence of dissolved oxygen. In addition to ROS, other strong oxidizing agents such as ammonium persulfate $(NH_4)_2S_2O_8$ and sodium periodate ($NaIO_4$) have shown effective catalysis for the PDA self-polymerization. The presence of $(NH_4)_2S_2O_8$ in neutral solution has shown an increase in polymerization rate to as high as 35 nm/h,[13] while $NaIO_4$ accelerated the polymerization rate to 90 ± 5 nm/h.[14] In addition to the PDA deposition, a rapid and homogeneous coating of TA using $NaIO_4$ in slightly acidic buffer as the catalyst was reported by Wang et al.[15]

2.2. Assembly of Metal-Phenolic Networks and Polymer-Phenolic Networks

Metal-phenolic networks (MPNs), generated from metal-polyphenol interaction, are also known to form a robust and versatile coating of polyphenols. MPNs have several advantages including high stability, high flexibility of thickness control, tailorable chemical composition, and substrate independence (Figure 1B).[16] It is worth noting that MPNs can be converted between mono-complex, bis-complex and tris-complex based on pH levels, for which more acidic condition causes a slow disassembly of the network. Taking this into account, pH-controlled delivery systems can be constructed. MPNs are normally fabricated by simple batch mixing of metal ions and polyphenols of choice under controlled pH. The one-step TA-Fe^{3+} MPNs reported by Caruso et al. led to a film thickness of 7.7 ± 0.4 nm to 11.9 ± 1.2 nm at the Fe^{3+}/TA (C_{TA}= 0.24 mM) ratios of 1:4, 1:3, and 1:2 at pH~7.[4] The same team then extended the one-step assembly to various combinations of metal ions and polyphenols with the film thickness adjusted by reaction time and molar ratios of metal and polyphenols.[17] This approach to MPNs coatings is scalable and cost-effective. More recently, multistep assembly was applied to fabricate MPNs. The coating was prepared by sequentially incubating the substrates with polyphenol solution and metal ion solution, respectively.[18] It was reported that the MPNs formed by multistep assembly has higher metal proportion than the on-step assembly. More specifically, 50 mol% of Fe in TA-Fe^{3+} MPN in multistep assembly is reported compared to only 25 mol% of Fe in the MPN for one-step assembly, leading to a lower Young's modulus in the multistep assembly because of the lower percentage of crosslinked TA moiety, giving rise to a high stiffness by the one-step MPN assembly.[18]

In addition to MPNs assembly, polyphenols can coordinate with biomolecules or synthetic polymers to form polymer-phenolic networks, allowing for layer-by-layer deposition of polymer/polyphenols conjugations (Figure 1C) with high uniformity of surface morphology, adjustable thickness and prolonged stability [19] Owing to a relatively high pKa, polyphenols can form either hydrogen bond with neutral polymers or electrostatic interaction with positively charged polymers in addition with covalent bonds and π-π stacking. For example, based on the reaction of quinone groups in polyphenols with amino groups, Lee and co-workers demonstrated that PG and polyethyleneimine (PEI) can crosslink through covalent bond to form a robust PG/PEI film,[20] leading to strong mechanical robustness and versatile adhesion.

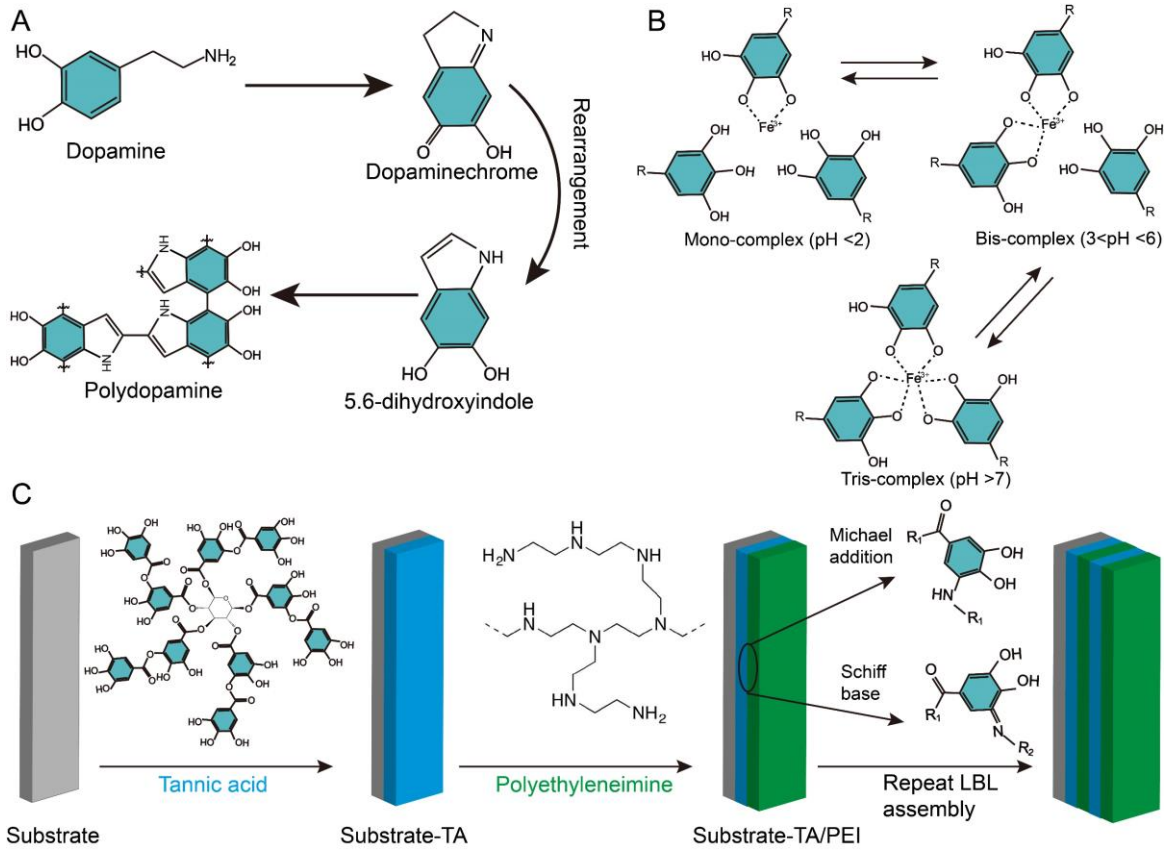

Figure 1. (A) self-polymerization of dopamine to form PDA coating. (B) coating of Fe^{3+}/TA networks. (C) LBL deposition of TA and PEI.

3. Controlled Surface Properties of Polyphenol-Based Coatings

3.1. Controlled Surface Functionality

The metal ions chelating and reducing property of polyphenols allow the coatings to convert noble metal ions such as Au^{3+}, Pd^{2+}, and Ag^{+} to metal nanoparticles and then stabilize the nanoparticles by binding to metal atoms on the nanoparticle surface. The universal adhesion of polyphenol coatings also can mediate the structural integration of different nanostructures. Duan et al. have shown that nanoparticles of different chemical nature coated with PDA can support the deposition of Au nanoparticles (NPs) and metal-organic frameworks (MOFs) (Figure 2A),[21] leading to multifunctional systems with synergistic properties. The modification of polyphenols with other molecules and polymers via covalent conjugation allows the polyphenol coated surfaces to act as the intermediating layer for the introduction of additional polymer-based functional coatings. For example, Zhang et al. used PDA coating as the intermediate layer to introduce PEI via the Schiff-base or Michael addition reaction, followed by ring-opening reaction to introduce zwitterionic poly-(2-methacryloyloxyethyl

phosphorylcholine-*co*-glycidyl methacrylate) (poly(MPC-*co*-GMA)) for designing a natural lubrication and antibacterial coating on bioimplants.[22] On the other hand, surface grafting of polymer brushes via atom transfer radical polymerization (ATRP) is a promising pathway to further modify polyphenol-based coatings.[23] Optical property of polyphenol-based coatings is an interesting aspect to discuss. PDA and MPNs have a broad spectrum across the UV−vis and near-infrared (NIR) wavelength range. The adsorption of PDA is attributed to the oxidation and self-polymerization process, while the adsorption of MPNs originates from the complex of polyphenol and metal ions. The strong irradiation absorption of polyphenols is of interest in the field of photothermal conversion.[24] It was shown that the coating of mesoporous PDA has enhanced UV-vis-NIR absorption of plasmonic Au NPs,[25] which exhibit a high photothermal conversion of 45.8% under 1 Wcm^{-2} NIR irradiation for 5 min (Figure 2B).

3.2. Controlled Surface Wettability

Benefitting from the diverse structure and chemical reactivity of polyphenols, coatings generating from PDA and plant polyphenols can tailor surface wettability of pristine materials, resulting in new perspectives in surface engineering. For example, during the investigation of DA polymerization, Lee et al. found that PDA coating turned the pristine hydrophobic surface into hydrophilic due to the abundant hydroxyl groups in its structure.[2] Ball et al. further found that oxidant-induced polymerization of DA generated a high content of carboxylic groups, which even tuned a hydrophobic surface into superhydrophilic.[14] In another report, Duan et al. deposited layers of oxidation-induced PDA nanoparticles onto both hydrophobic kapok fibers and hydrophilic cotton fibers.[26] The modified fibers exhibited dual-superlyophobicity (concurrent under-oil superhydrophilicity and under-water superoleophobicity). Furthermore, they have investigated the surface co-deposition of other polyphenols with 3-aminopropyltriethoxysilane (APTS). The silane hydrolyzed along with polymerization of polyphenols resulted in surfaces with interesting super-repellent properties, in which the surface can be wetted by a broad range of liquids and the wetted surface became repellent to any liquids that are immiscible with the original wetting liquids (Figure 2C).[27]

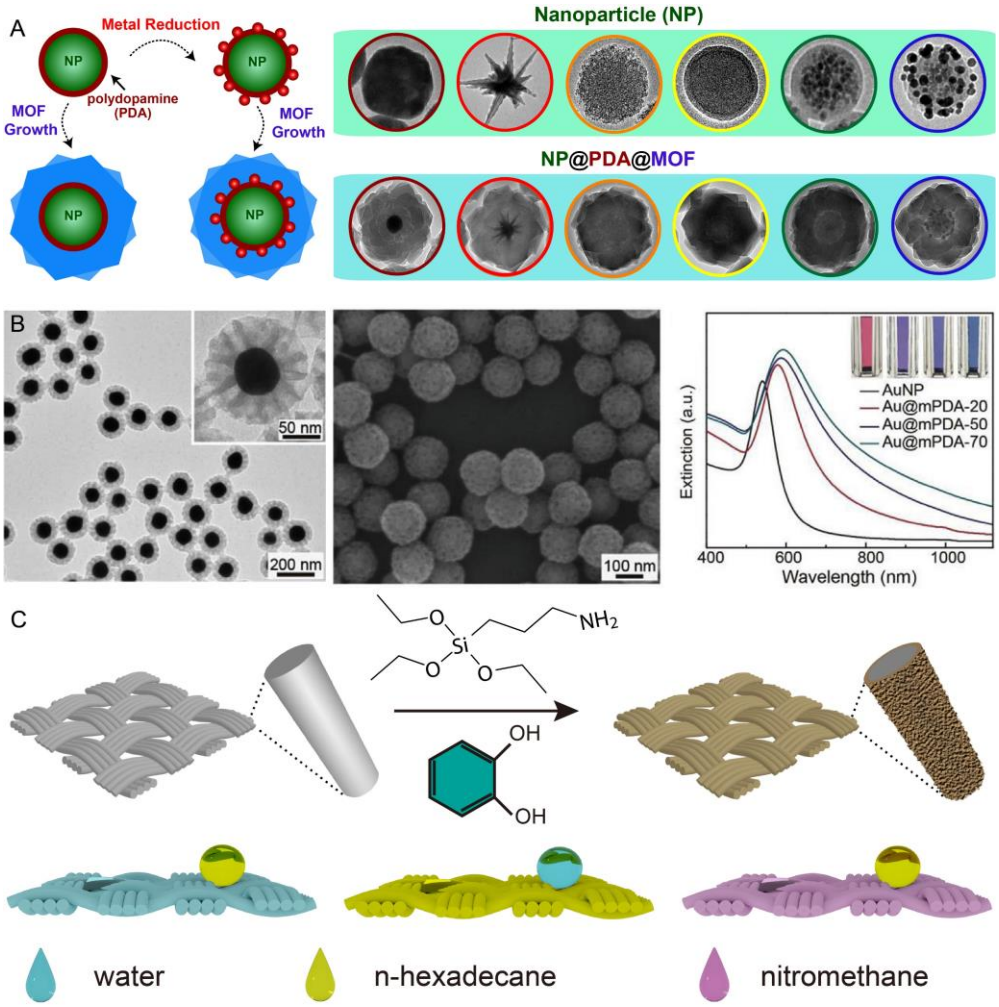

Figure 2. (A) Schematic illustration of PDA coated nanoparticles and deposition of Au and MOF. Reprinted with permission from Reference 21. Copyright 2018, American Chemical Society (B) Preparation of Au@mPDA nanoparticles and its UV-Vis absorption. Reprinted with permission from Reference 25. Copyright 2021, Royal Chemical Society. (C) Schematic illustration of membrane functionalized by co-deposition of APTS and polyphenols and the universal liquid repellency. Reprinted with permission from Reference 27. Copyright 2021, American Chemical Society

Surface wettability of polyphenol-based coating can also be controlled via post-functionalization. As mentioned above, polymers and molecules with thiols or amines termination can react with catechol groups of polyphenol coatings via Michael addition/Schiff-base reactions. Hyperbranched PEI with abundant primary, secondary and tertiary amino groups not only provides more hydrophilic amine groups but also accelerates the deposition process of polyphenols.[28] Second, the catechol groups in polyphenols can induce mineralization to form additional functional coatings. For example, Duan et al. employed PDA coating as a mediated layer to introduce low surface energy molecules via condensation of silane so that the modified surfaces can exhibit either superhydrophobicity, superlyophobcity or superamphiphobicity, which showed repellency towards a wide range of

liquids with different surface tensions.[29,30] These examples highlight that polyphenol-based coatings provide versatile functionalities in terms of controlling surface wettability to produce various wetting states, regardless of the pristine wetting behavior.

4. Applications of Phenolic-Based Coatings

4.1. Coatings on Medical Devices for Biofunctionality

Implant-associated infections (IAI) are serious side effects of implantation surgery and constitute a serious threat to human health worldwide. Particularly, the development of three-dimensional biofilms caused by the colonization of planktonic bacteria continues to be a significant problem in the healthcare industry. Additionally, biofouling by proteins, bacteria, and fungi has a number of detrimental consequences, including the failure of implants and medical devices. The most common treatment method for IAI is to replace implants with new ones or to administer systemic antibiotics immediately following surgery. In surgical replacements, there is a chance of recurrent infection, which would extend the healing process and raise patient morbidity. Antibiotics remain the mainstay to combat bacterial infections, but their indiscriminate usage has led to the emergence and predominance of multidrug-resistant (MDR) superbugs. Efforts have been made to fabricate functional coatings for antibacterial effects without using antibiotics. However, current coating technologies such as chemical conjugation, physical grafting, and plasma-supported deposition are lack of general applicability and suffer from material dependency.[31] Polyphenols-based materials have attracted increasing attention as an alternative antibacterial agents to combat MDR bacteria. Metal ions reduction property of polyphenols allows for the deposition of metal NPs such as Ag NPs on the polyphenol coatings. The slow release of Ag^{+} exhibits a long-term antibacterial action for implantable devices by a contact-killing basis.[32] In addition, cationic polymers are potential candidates to treat bacteria by contact-killing mechanism due to the bacterial membrane disruption. Zhou et al. reported that cationic polymers synthesized on PDA-coated catheter can achieve 98.88% and 94.51% reduction of methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcusfaecalis (VRE)), respectively.[33] Furthermore, strong NIR adsorption of polyphenols imparts coatings that allow for photothermal killing of bacteria. Wang et al. showed that the temperature of TA/Fe^{3+} coating can increase to above 60 ^{o}C under a 2.2 Wcm^{-2} of NIR irradiation within 5 min, leading to the killing of more than 99% of bacteria.[34]

Besides antibacterial ability, antibiofouling coating is also crucial for protecting medical devices. The hydrophilic polyphenol layers can function as protective coatings to reduce fouling caused by proteins and bacteria due to their inherent fouling resistance capabilities generated from the hydration layer that resists foulants.[35] However, the presence of aromatic rings in their structure limits the hydrophilicity of the polyphenol coatings and cause reduced anti-biofouling ability. Furthermore, antibacterial ability of polyphenols themselves is relatively weak. Therefore, incorporation with other molecules were sought to enhance antibiofouling effect of the coatings. For example, Caruso et al. showed that the introduction of galloyl-modified poly(2-ethyl-2-oxazoline) onto TA/Fe^{3+} multistep coatings can reduce absorption of proteins such as bovine serum albumin, immunoglobulin G and fibrinogen by 79%, which is comparatively higher than the MPN coating alone.[36] Superhydrophilic surfaces based on mussel-inspired modification are commonly applied to address biofouling issue. The steric effect and substantially charged groups of hydrophilic compounds in superhydrophilic surface form the basis of their fouling-resistant property due to the high energetic barrier of removing the hydrated layer during the attachment of proteins and microbes.[37] As such, grafting of zwitterionic and highly hydrated neutrally charged polymers such as poly(ethylene glycol) and poly(vinyl alcohol) on the polyphenol coatings are the ideal solution for additional surface functionalization of superhydrophilic antibiofouling.[38-41] Superhydrophobic and superamphiphobic surfaces are also promising candidates for biofouling resistance because the stable air cushion trapped underneath the hierarchical structure impedes the contact angle between liquids and solid surface, enabling the easy roll-off of liquids and nonfouling of biological agents. However, the air cushion is unable to withstand a high pressure of liquids or a mechanical damage, resulting in the deterioration of liquid superrellency. Slippery liquid infused porous surface (SLIPS) has recently attracted considerable attention in antibioflouling application due to its potential in the stable liquid repellency even under a harsh condition.[42] Aizenberg et al. first showed that the as-prepared SLIPS can prevent 99.6% of *Pseudomonas aeruginosa*, as well as 97.2% of *Staphylococcus aureus* and 96% of *Escherichia coli* biofilm attachment over a 7-days period, under both static and physiological realistic flow conditions, which was superior to the control superhydrophobic surface.

Controlled wettability of polyphenol-based coatings is also crucial for synergistic antibacterial/antifouling effects, which are beneficial for continuous discharge of bactericidal agents and self-cleaning surface. Wang et.al deposited poly(N-isopropylacrylamide) (PNIP), a thermal responsive polymer, on TA/Fe^{3+} coatings via Michael additional reaction (Figure

3A).[34] Under NIR exposure, bacteria are efficiently killed by localize photothermal heating. However, at the temperature higher than 37°C, PNIP undergoes the hydrophilic to hydrophobic transition due to lower critical solution temperature, which promotes bacterial adhesion. When laser was off, PNIP-modified surface at lower temperature became superhydrophilic, thus enhancing the release of dead bacteria. This on/off laser irradiation can make the surfaces display synergistic killing/release performance. Yu et al. reported a zwitterionic and antibacterial MPN coated contact lens based on the coordination of Cu^{2+} and poly(carboxylbetaine-co-dopamine methacrylamide) copolymer.[43] Cu^{2+} played the role as a bactericidal agent, while the copolymer showed excellent antifouling of bacteria due to its superhydrophilicity (Figure 3B).

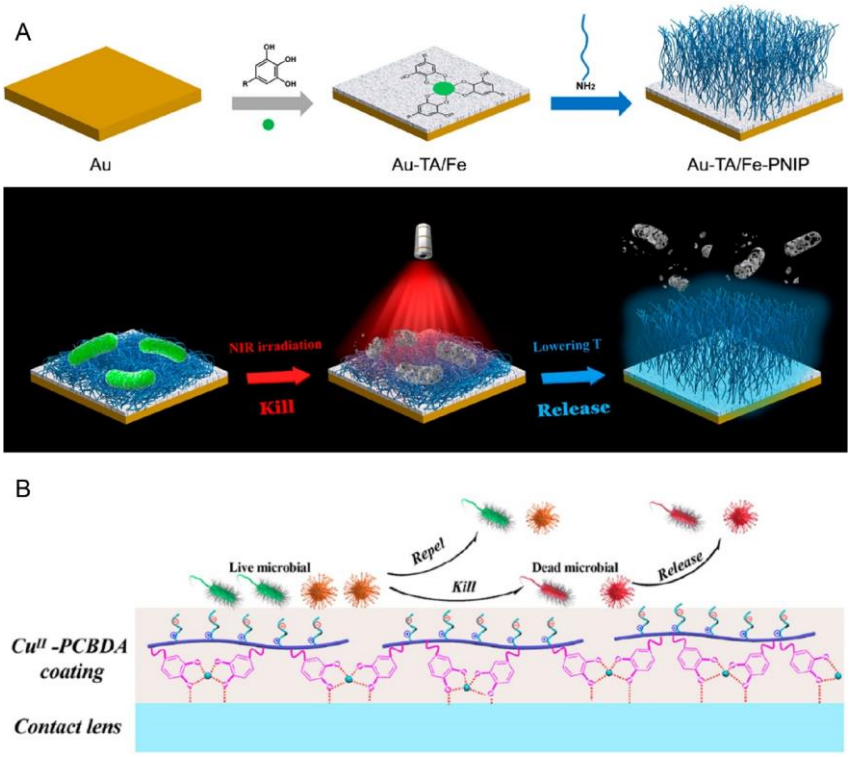

Figure 3. (A) fabrication of dual photothermal bacterial-killing and thermal triggered bacterial-release of PNIP modified TA/Fe^{3+} coating. Reprinted with permission from Reference 34. Copyright 2019, American Chemical Society. (B) preparation of a dual-function coating of Cu^{2+}-PCBDA on contact lens that shows synergistic kill-release effect of bacteria. Reprinted with permission from Reference 43. Copyright 2020, American Chemical Society.

4.2. Surface Coatings for Therapeutic Delivery and Biosensing

The controlled distribution of bioactive compounds with the promising activity is of great importance for therapeutic effects. Conventionally, the direct delivery of therapeutic and other active payloads in vivo is plagued by intrinsic problems such as poor stability, poor solubility,

unfavorable pharmacokinetics, and nonspecific toxicity. Recent development in nanomedicine has centered on the development of strategies for the controlled delivery of payloads with enhanced efficacy and reduced side effects. As therapeutic carriers, stimuli-responsive nanoparticles provide numerous advantages, including protection of payloads, prolonged circulation time, and improved accumulation at disease locations. To date, a range of endogenous and exogenous stimuli have been used to trigger the release of payloads with precise spatiotemporal control overdoses in nanomaterial-based delivery systems. Exogenous stimuli include externally applied light, ultrasound, heat, electric or magnetic fields, and mechanical stress, while endogenous stimuli typically are pH, ionic strength, enzyme activity, and redox reactions. Exogenous stimuli are not dependent on intracellular conditions, which can vary between individuals and illness sites. Among the external stimuli listed above, light has garnered particular interest due to its ease of operation, high adaptability, low invasiveness, and great spatiotemporal control. NIR irradiation has greater tissue penetration and minimal phototoxicity to normal cells and tissues, which bodes well for its clinical application. Duan et al. recently showed that the compact size of hyperbranched Au plasmonic blackbody (AuPBs) made from *in situ* reduction of Au^{3+} by DA exhibited an excellent photothermal efficiency of >80% and closely matched photothermal activity in both first and second window NIR (NIR-I and NIR-II) spectra.[44] The NIR-II irradiation applied on the Au PBs had a higher maximum permission exposure than NIR-I irradiation, showing better tumor ablation efficiency (Figure 4A). They have demonstrated that mesoporous PDA (mPDA) coated AuPBs (Figure 4B) gave rise to efficient loading with protein payloads, in which mesopores pf mPDA served as reservoir to load DNase I enzyme.[45] Under the NIR-II irradiation, DNase I is released and disrupted neutrophil extracellular traps (NETs), leading to enhanced contact between tumor and immune cells and improved immunotherapy.

Polyphenol-coated nanomaterials has also been widely used for the sensing of a broad spectrum of targets from small molecules (e.g., metal ions and small molecules) to large analytes (such as biomacromolecules, virus, and bacteria). First, the bioconjugation capability of polyphenol molecules has allowed their substantial uses in the convenient biofunctionalization of biosensor surfaces with targeting ligands such as antibodies, aptamers, and small molecular sensing elements, or for the direct detection of electroactive molecules. Moreover, the multivariate polyphenolic chemistry including redox chemistry, coordination chemistry and bioconjugate chemistry can collectively guide the design of nanostructures for biosensing applications. Notably, the PDA coating can play multiple roles in the development

of biosensors. Duan's group recently reported a PDA-mediated strategy for tailored enhancement of fluorescence resonance energy transfer (FRET).[46] First, the adhesive property of PDA allowed surface-modification on different plasmonic nanoparticle substrates with precisely engineered spectral properties. Second, the amphiphilic nature of PDA enabled self-assembly of the nanoparticles at the water-oil interface, enabling the immobilization of closely packed nanoparticle array onto flat substrates. Third, the accurately controlled thickness (5~25 nm) of the PDA shell made it a tunable nanoscale spacer between the fluorophores and plasmonic surfaces. Finally, bioconjugation on the PDA surface was straightforward via Michael addition and Schiff-base reactions. These synergistic characteristics enabled the preparation of plasmonic substrates of desired optical properties to match the excitation/emission spectra of any fluorophore of interest. Therefore, customized plasmonic substrates can be designed and functionalized with a DNA molecular beacon with a Cy3/Cy5 pair for improved FRET efficiency in a DNA microarray assay, leading to an increased sensitivity of 0.74 nM towards the target DNA sequence from *Listeria monocytogenes* (Figure 4C).

It is well known that many natural enzymes require metal ions (e.g., Fe^{2+}, Cu^{2+}, Mn^{2+}, Zn^{2+} and Ca^{2+}) or metal-based cofactors to implement their catalytic function. Interestingly, some metal-doped polyphenol/PDA coatings and nanostructures have been found with enzyme-like catalytic property, providing a series of nanozymes with oxidoreductase-mimicking activities that can be employed as the biological sensing components of biosensors.[47] Since the phenolic coatings allow convenient surface functionalization, natural enzymes can be easily immobilized onto the metal-phenolic nanozymes to produce various multienzyme cascade systems. Notably, the integration of multienzyme systems into biosensors could expand the spectrum of detectable substances and enhance the sensitivity of biosensors. Very recently, Duan and coworkers developed a nanozymatic magnetic nanomixer with an efficient mixing capability and hence improved peroxidase-like activity by forming Fe^{2+}-doped PDA coating on the surface of well-aligned magnetic nanoparticles. Multiple oxidases including glucose oxidase, cholesterol oxidase and uricase were further immobilized on the surface of the magnetic nanozyme (MNE), resulting in the formation of various multienzyme cascade systems.[48] Interestingly, the MNE-based multienzymes displayed increased overall activities via active rotation under an external magnetic field. These self-mixing multienzyme systems were further used to catalyze colorimetric reactions on a homemade microchip for the visual multiplexed detection of glucose, cholesterol and uric acid

(Figure 4D), allowing a point-of-care testing with low sample consumption, short assay time, wide detection range and high sensitivity.

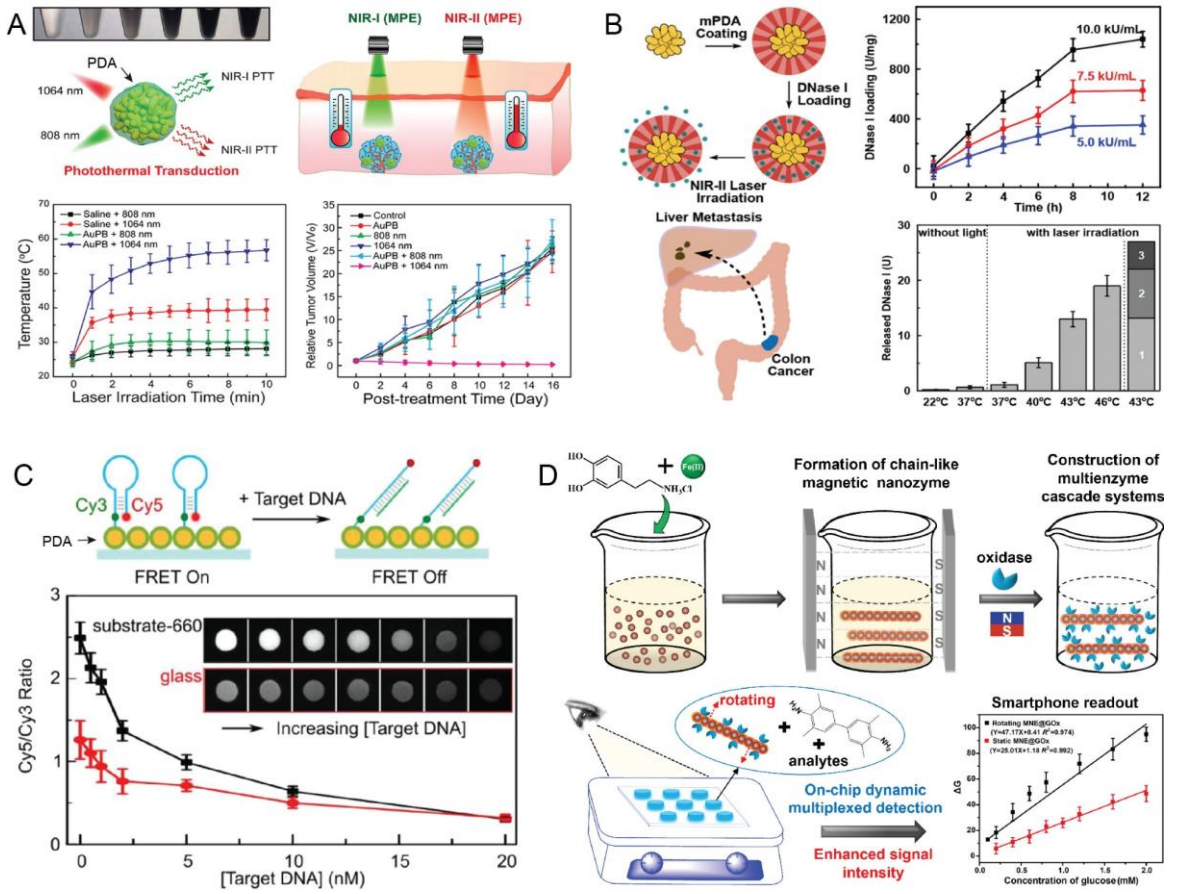

Figure 4. (A) preparation of Au BPs and the tumor ablation under NIR irradiation. Reprinted with permission from Reference 44. Copyright 2018, American Chemical Society. (B) Preparation of mPDA coated Au BPs for enzyme delivery. Reprinted with permission from Reference 45. Copyright 2022, American Chemical Society. (C) Cy3/Cy5 pair-based FRET on a plasmonic substrate for detection of the target DNA sequence from *Listeria monocytogenes*. Reprinted with permission from Reference 46. Copyright 2020, Wiley-VCH. (D) Nanozymatic magnetic nanomixers for enzyme immobilization and on-chip colorimetric detection of metabolic disease biomarkers. Reprinted with permission from Reference 48. Copyright 2022, Elsevier.

5. Conclusion and Perspective

Phenolic-based coatings with universal adhesion and intrinsic reactivities for chemical modification have received growing attentions in the design of hybrid functional materials with unique combinations of physiochemical properties for biomedical applications. In this Perspective, well-established approaches to forming robust polyphenolic surface coatings in conjunction with active payloads have been discussed. We also summarize the physiochemical

interactions and their functions in the coatings as well as the diverse chemistry to further modify the surfaces. Polyphenol coatings hold promise in clinical translation as a class of multifunctional, tailorable surface coating that are adaptable to virtually any solid substrates. The full potential of polyphenol-based coatings remains to be explored.

Polyphenolic coatings as a multifunctional "bioglue" not only can impart their bioactivities such as antibiofouling, antioxidant, and metal-based nanozymic properties to a broad range of biomaterials and medical devices, also provide opportunities for structural integration of chemically dissimilar building blocks for synergistic functionalities. Assembly of polyphenols and other biomolecules with precise spatial controls offers emerging applications that require synergistic actions such as cascade biocatalysis, combination therapy, molecular and cellular detection, and theranostics.

In particular, the ability of MPN to introduce and modulate the nanozymic properties on solid substrates is of broad interest for diagnostic and therapeutic applications based on the enzyme-mimicking activities. The universal adhesion of polyphenolic coatings allows customized combination of functional substrates and nanozymes, with additional flexibilities to introduce complementary functional moieties, providing potential solutions to major medical challenges such as biofilm growth on medical devices. Therapeutic formulations can benefit from the antifouling surface modifications for improved disease targeting and the possibilities of combinational therapy with different treatment modalities such as chemotherapy and immunotherapy. Medical translation of the polyphenolic coatings relies on the scale-up production of the modified surfaces based on well-established manufacturing methods such as roll-to-roll coatings and spray coating. Matching the rate of coating generation with these manufacturing processes is of critical importance for this effort. Notably, the impact of polyphenolic compounds and the resulting coatings on cellular activities have not been systematically reviewed yet.

Controlling the transportation of biofluids is of importance for wound healing process. Conventional dressings of either hydrophilic or hydrophobic behavior are facing difficulties in wound fluid management, suffering from the failure of removing excessive biofluids that easily overhydrate the wound side. Janus membranes with asymmetric wettability have shown their unique unidirectional fluid and ion backflow transportation.[49] The ability of polyphenol coatings to immobilize bactericidal agents and bioactive ions for diagnostics and therapeutics is of great potential for infection treatment and monitoring. Combining the unique properties

of Janus membranes in fluid harvesting and functional coatings of polyphenols therefore would be beneficial for the management of chronical wounds.

Acknowledgements

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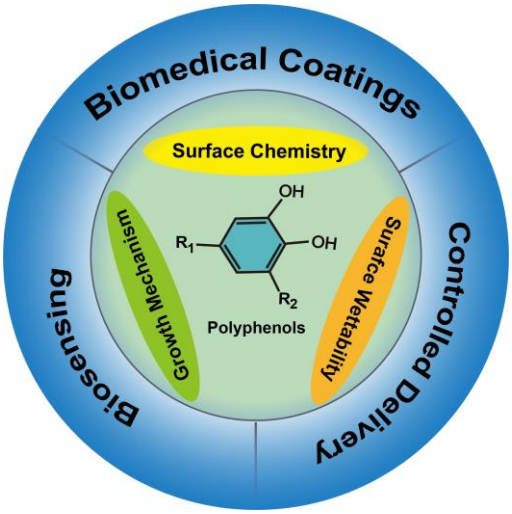
TOC Graphic


Biomedical Coatings
Controlled Delivery
Biosensing
Surface Chemistry
OH
R1
OH
R2
Polyphenols
Growth Mechanism
Surface Metallicity

Biographies:

Van Cuong Mai received his BSc in chemistry from Vietnam National University, Hanoi in 2014. He completed his Ph.D. in material chemistry in 2019 at Nanyang Technological University under the supervision of Prof. Hongwei Duan. He is now working with Prof. Hongwei Duan as a research fellow in School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University. His current research interest focuses on polyphenols-based materials with tailorable wettability for biomedical applications.

Li Di received her PhD degree from School of Food Science and Technology, Jiangnan University under the supervision of Prof. Li Liang in 2021. She studied at Prof. Duan Hongwei's group as a visiting PhD student for two years from 2019. She is now working with Prof. Hongwei Duan as a research fellow in School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University. Her current research interest focuses on metal-phenolic nanomaterials with enzyme-mimicking properties for biosensing, tumor therapy, and immunotherapy.

Hongwei Duan is currently a professor in the School of Chemistry, Chemical Engineering and Biotechnology, Nanyang Technological University. He received his B.S. in applied chemistry and M.S. in polymer chemistry & physics at Fudan University. After completing his Ph.D. at the Max Planck Institute of Colloids and Interfaces, he had postdoctoral training in the joint Department of Biomedical Engineering at Emory University and Georgia Institute of Technology. His current research focuses on understanding the surface/interface properties of micro- and nano-structures to achieve tailored optical, electronic, magnetic, and structural properties for biomedical and environmental applications.