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Mini-Review

Oxidation Chemistry of Catechol Utilized in Designing Stimuli-Responsive Adhesives and Antipathogenic Biomaterials

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ABSTRACT: Mussel foot proteins (Mfps) contain a large amount of the catecholic amino acid, DOPA, allowing the marine organism to anchor themselves onto various surfaces in a turbulent and wet environment. Modification of polymers with catechol imparts these materials with a strong, wet adhesive property. The oxidation chemistry and oxidation state of catechol are critical to the design of synthetic adhesives and biomaterials. In this Mini-Review, the effect of catechol oxidation state on adhesion, oxidation-mediated catechol cross-linking, and the generation of reactive oxygen species (ROS) during catechol oxidation are reviewed. Finally, the tuning of catechol oxidation state in designing stimuli-responsive adhesives and the utilization of ROS byproducts for antimicrobial and antiviral applications are reviewed.

1. INTRODUCTION

Marine mussels are one of nature's experts at wet adhesion, achieving strong and durable attachments to a variety of surfaces in their chemically heterogeneous habitat.[1] Mussels secrete mussel foot proteins (Mfps) to form byssal threads and adhesive plaques, allowing them to adhere onto various surfaces (e.g., rock, wood, metallic surface, sea creature shell, etc.) in a wet environment (Figure 1). One of the key constituents of Mfps is the amino acid 3,4-dihydroxy-L-phenylalanine (DOPA). DOPA contains a catechol side chain, which is capable of forming a wide range of reversible (e.g., hydrogen bonding, cation-π interaction, metal ion complexation) and irreversible cross-linking chemistries.[2] This diversity in catechol chemistry has led to the development of various catechol-containing bioadhesives and biomaterials for a wide range of applications.[3,4]

Oxidation induced covalent cross-linking and polymerization is one of the often used catechol chemistries in designing *in situ* curable and injectable bioadhesives as well as robust, covalently cross-linked coatings.[4,5] To activate catechol for cross-linking, catechol needs to be oxidized into its reactive quinone form. During the process of catechol oxidation, reactive oxygen species (ROS) are generated as byproducts.[3] ROS has been found to have both beneficial (e.g., promote wound healing, disinfectant) and deleterious (e.g., retard healing) biological effects depending on its concentration and the biological system that comes in contact with the ROS.[6] Therefore, ROS concentration needs to be regulated depending on the application. Additionally, the interfacial bonding strength of catechol is highly dependent on its oxidation state.[7] As such, understanding the oxidation chemistry of catechol is critical to the function and design of catechol-based adhesive and biomaterial.

The use of catechol in designing polymeric materials for various applications such as bioadhesives and antifouling coatings have been the subject of numerous review papers.[1−4] This Mini-Review focuses on the utilization of catechol oxidation chemistry and the control of catechol oxidation state in two relatively new areas of research: (1) designing stimuli-responsive adhesives with tunable adhesive property and (2) the use of ROS byproduct of catechol oxidation for antimicrobial and antiviral applications. Here, we first reviewed the effect of catechol oxidation state on adhesion, oxidation-mediated catechol cross-linking, and the generation of ROS during catechol oxidation. Then, we introduced the catechol-based stimuli-responsive adhesives and ROS-releasing biomaterials.

2. CATECHOL OXIDATION CHEMISTRY

The oxidation state of catechol critically affects its function as an adhesive moiety and a cross-linking precursor. These factors affect the use of catechol for designing an *in situ* curable adhesive. Additionally, ROS is generated during the process of catechol oxidation. In this section, we review the effect of the oxidation state of catechol and its effects on surface adhesion, oxidation-mediated cross-linking of catechol, and ROS generation during catechol oxidation.

2.1. Oxidation State and Surface Interaction. The oxidation state of catechol critically affects its interfacial bonding property. In its reduced form, catechol exhibits enhanced interfacial adhesion strength to inorganic surfaces through the formation of coordination and hydrogen bonds. The bonding strength of catechol with titanium has been reported to average around 800 pN.[7] When catechol is

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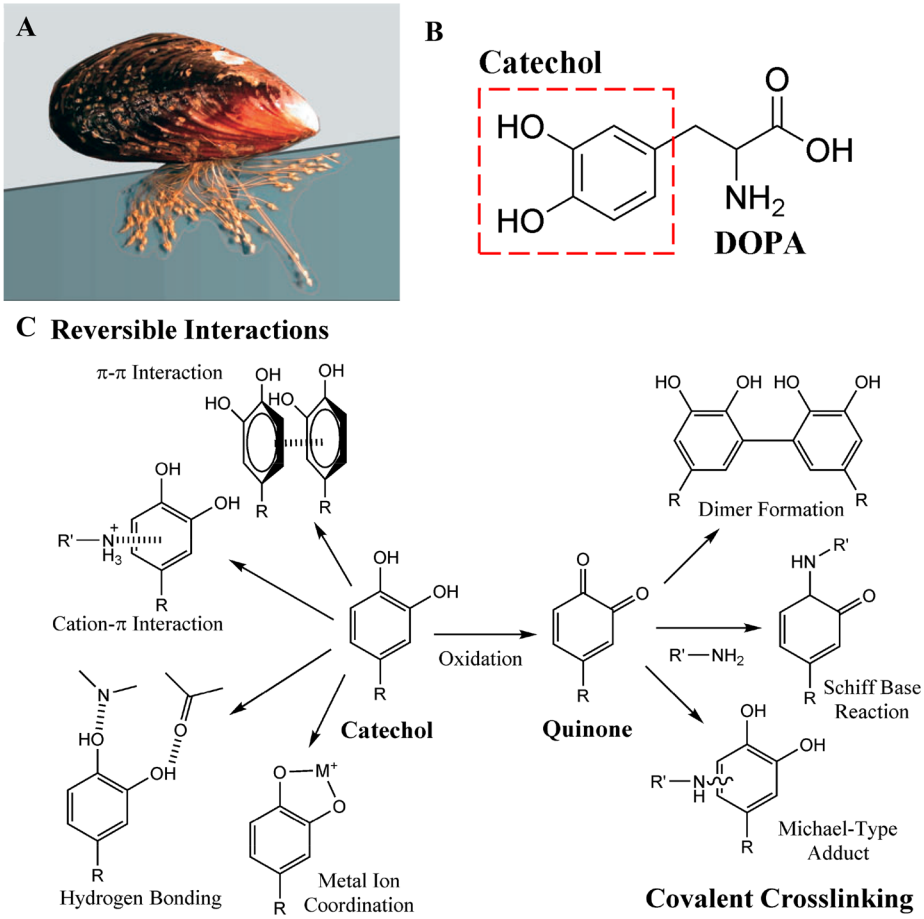

Figure 1. Photograph of the marine mussel, *Mytilus californianu* (A). Reprinted with permission from ref 1. Copyright 2011 Annual Reviews, Inc. Chemical structure of DOPA with a catechol side chain (B). Diverse chemistry of catechol (C).

oxidized to its quinone form, the measured adhesion strength was reduced by 80%. The pH of the surrounding medium is one of the main factors in controlling the oxidation state of catechol. In an acidic pH (pH = 3), catechol exhibits strong adhesion, and this value decreases with increasing pH because of catechol oxidation.[8] In nature, mussels control adhesion by using different antioxidant proteins consisting of cysteine (i.e., Mfp-6) to preserve the reduced form for adhesion in a basic condition of the marine environment (pH 7.5−8.4).[3] In a synthetic adhesive system, incorporating anionic side chains such as acrylic acid to buffer the local pH within the adhesive network has been demonstrated to preserve the reduced form of catechol for enhanced adhesion at a neutral to basic pH.[9] Additionally, chemical modification of catechol with an electron-withdrawing group (EWG) (e.g., nitro group) lowered the dissociation constant pK_a catechol hydroxyl group and was demonstrated to increased catechol's resistance to oxidation for surface bonding.[10]

When catechol is oxidized to its quinone form, quinone is highly reactive and can react with various nucleophilic functional groups (e.g., $-NH_2$, $-SH$, imidazole) found on biological substrates, forming an interfacial covalent bond.[7,9] Quinone forms Michael type adducts with these nucleophilic functional groups and Schiff base adducts with primary amines. Additionally, pH affects the availabilities of these nucleophilic groups for cross-linking as they become progressively more protonated in an acidic pH (e.g., pK_a of ε-lysine ~10).[11] While the pH of oxygenated tissue is around 7.4, other tissues such as dermal tissues and cancer tissues are more acidic and may affect the interfacial bonding between catechol and these tissue substrates. While the coupling between nucleophiles and catechol has been demonstrated in synthetic polymer systems, it has not been conclusively shown in native mussel adhesive proteins.

2.2. Oxidation-Mediated Catechol Cross-Linking.

Oxidation-mediated cross-linking is one of the key criteria for creating *in situ* curable adhesives and biomaterials. Catechol can be oxidized to its highly reactive quinone form through autoxidation and the use of enzymatic (e.g., tyrosinase, horseradish peroxidase) and chemical oxidants (e.g., sodium periodate).[12] The oxidized quinone is highly reactive and can polymerize to form oligomers with up to 6−7 catechol residues, resulting in the curing of catechol-containing adhesives. The oxidative cross-linking of catechol is dependent on multiple factors, including the type of oxidant, the concentration of oxidant, and the solution pH.[11,12] For enzyme-induced cross-linking, both the rate and degree of polymerization of catechol increased proportionately with enzyme concentration. For periodate-mediated cross-linking, a periodate-to-catechol molar ratio of 0.5−1 exhibited an elevated rate of cross-linking as the reduced form of catechol is required for cross-linking.[12] Additionally, the rate of periodate-mediated cross-linking increased with increasing pH, potentially because of the increased stability of the oxidation intermediates of catechol under mildly acidic conditions.[11] Most recently, electrochemical-induced oxidation

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and curing of catechol-containing adhesive were demonstrated.[13] Functionalizing catechol with EWG, such as a nitro group, drastically increased the rate of cross-linking.[14] EWG modification lowers the dissociation constants of the catechol hydroxyl groups from pK_a = 9.2 to pK_a = 6.6 for nitro-functionalized catechol, allowing fast catechol oxidation and cross-linking even under mildly acidic pH (5.7−6.7). However, because of steric hindrance, nitro-functionalized catechol formed only dimers, which reduces the mechanical property of the cured adhesive when compared with unmodified catechol that can polymerize to form oligomers.

2.3. Generation of ROS during Catechol Oxidation. Catechol generates ROS as a byproduct during the process of oxidation.[3] During catechol autoxidation in an oxygenated and alkaline medium, molecular oxygen oxidizes catechol to generate superoxide ($O_2^{\bullet-}$) (Figure 2).[15] $O_2^{\bullet-}$ is a potent

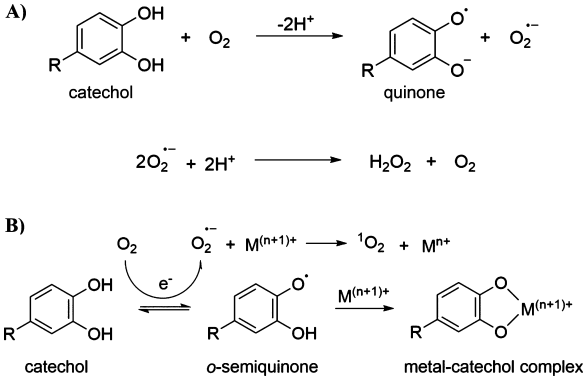

Figure 2. During autoxidation, oxidation of catechol to quinone generates superoxide radical ($O_2^{\bullet-}$) as a byproduct. $O_2^{\bullet-}$ can be further converted to the less reactive hydrogen peroxide (H_2O_2) in the presence of proton or water (A). During metal ion-mediated oxidation, oxidation of catechol to *o*-semiquinone generates $O_2^{\bullet-}$, which can subsequently form a metal ion-catechol complex (B). $O_2^{\bullet-}$ can be further oxidized into the more reactive singlet oxygen ($^1O_2$) by the metal ion. Adapted with permission from ref 19. Copyright 2020 American Society of Chemistry.

oxidant and can be further converted to hydrogen peroxide (H_2O_2) through the interaction with proton ions or additional catechol oxidation. Generation of H_2O_2 increases with increasing catechol concentration, pH, and temperature.[16] Additionally, H_2O_2 generation from the slow autoxidation of catechol can be sustained for over 4 days. Similarly, H_2O_2 is generated as a byproduct during periodate-mediated oxidation and cross-linking of catechol-containing adhesive.[17] Unlike autoxidation, H_2O_2 is only generated during catechol polymerization, which lasts around 6 h. H_2O_2 demonstrates various biological effects depending on its concentration and the type of tissue exposed to the H_2O_2. At moderate concentrations (10−1000 μM), H_2O_2 can promote wound healing and angiogenesis.[3] However, at higher concentrations, H_2O_2 can retard wound healing, damage healthy tissue, and increase the duration of the inflammatory response. Additionally, different cell types exhibit different levels of sensitivity to oxidative stress.[17] Hence, controlling the concentration of the released H_2O_2 is critical to an effective catechol-based bioadhesive and biomaterial design. Recently, porous silica nanoparticles were incorporated into catechol-containing adhesive to reduce the amount of released H_2O_2.[18] This nanocomposite adhesive demonstrated reduced cytotoxicity and promoted cellular proliferation in cells that are highly sensitive to ROS (e.g., tenocytes). Generation of ROS via autoxidation and chemical-induced oxidation occurs mainly at a neutral to basic pH. On the other hand, ROS generation through the oxidation of metal ions and nanoparticles can occur over a wider range of pH (pH 3−9).[19] During metal-mediated oxidation, $O_2^{\bullet-}$ is generated and further converted to form singlet oxygen ($^1O_2$) by the metal (Figure 2B).

3. CATECHOL OXIDATION-BASED APPLICATIONS

This section reviews two relatively new applications that utilize catechol oxidation chemistry. The first application involves the use of pH and electrochemical oxidation to control the oxidation state of catechol for developing a stimuli-responsive adhesive. In the second application, the ability of catechol to generate ROS during oxidation was utilized to design portable biomaterials for antimicrobial and antiviral applications.

3.1. Tuning Oxidation State of Catechol for Designing Stimuli-Responsive Adhesive. Stimuli-responsive adhesives exhibit tunable adhesive properties when exposed to different environmental stimuli (e.g., pH, temperature, electricity, etc.). These adhesives have many potential applications in the biomedical field (e.g., painless removable wound dressings, temporary adhesive for prosthetics, etc.) as well as various industries (e.g., removable parts, shape-memory materials, soft robotics, etc.).[20] However, most stimuli-responsive adhesives are designed to bond to dry surfaces and have limited reversibility between their adhesive and nonadhesive states. Tuning the oxidation state of catechol has emerged as a novel approach to design stimuli-responsive adhesive that can adhere to wet surfaces.[21] In this approach, the reduced form of catechol provides strong interfacial bonding while the oxidized form exhibits weak adhesion. However, the oxidized quinone is also highly reactive and can result in irreversible cross-linking with limited reversibility. A temporary protecting group in the form of phenylboronic acid was introduced in the adhesive, and the adhesive exhibits strong adhesion at acidic pH (pH 3) and weak adhesion at basic pH (pH 9) as a result of catechol-boronate complex formation (Figure 3). Acrylic acid can be incorporated to tune the complexation pH so that the adhesive exhibits strong adhesion even at a mildly basic pH (pH 7.5−8.5), while

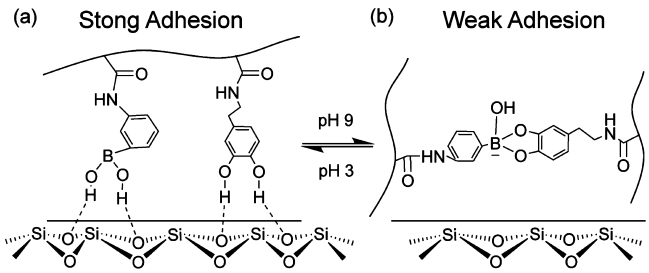

Figure 3. Schematic representation of stimuli-responsive adhesive containing catechol and phenylboronic acid functional groups. The adhesive demonstrates strong adhesion in acidic pH as both the catechol and phenylboronic acid contribute to interfacial bonding (a). The adhesive demonstrates weak adhesion at basic pH as a result of catechol-boronate complexation (b). The network-bound phenylboronic acid acts as a temporary protecting group to prevent catechol oxidation and to preserve the reversibility of the adhesive. Reprinted with permission from ref 21. Copyright 2016 American Chemical Society.

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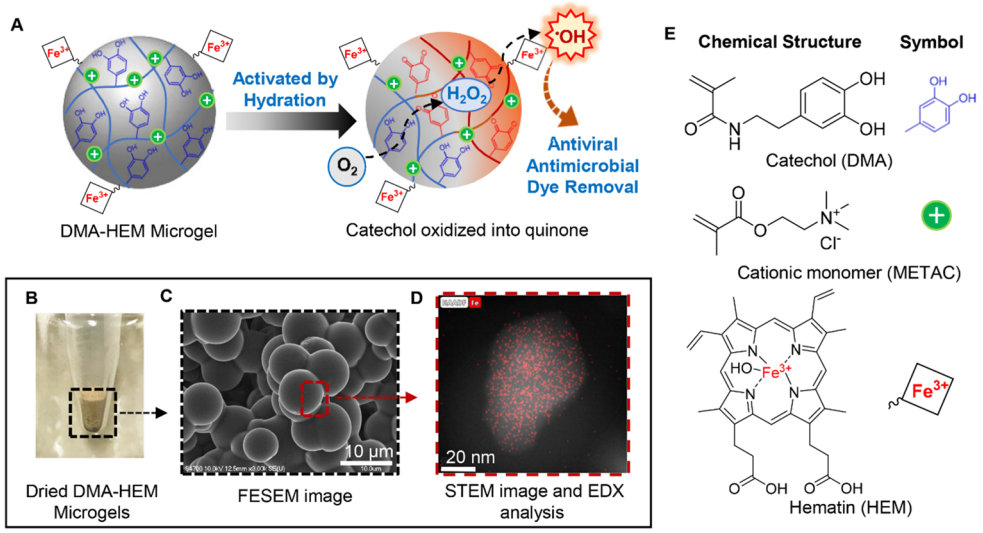

Figure 4. Schematic representation of the activation of dopamine methacrylamide (DMA) and hematin (HEM) containing microgel to generate •OH through catechol oxidation (A). Photograph (B) and field emission scanning electron microscopy (FESEM) image (C) of microgels. Scanning transmission electron microscopy (STEM) image and energy-dispersive X-ray (EDX) analysis confirmed HEM functionalization based on the presence of iron (red dots) on the surface of the microgels (D). Chemical structure of monomers used to prepare DMA- and HEM-containing microgels (E). Adapted with permission from ref 25. Copyright 2020 American Chemical Society.

preserving the pH-responsive adhesive property.[22] Coating the catechol and phenylboronic adhesive onto an array of micropillars enhanced the rate of transition of the adhesive between its adhesive and nonadhesive states, presumably because of the increased surface-to-volume ratio for the diffusion of ions needed to change the pH within the adhesive network.[23]

Using pH as an externally applied stimulus to tune adhesive property is slow and impractical. Recently, a study demonstrated that it is feasible to deactivate a catechol-containing adhesive using electrochemical oxidation.[24] Model catechol-containing adhesive was brought into contact with a titanium surface, which also served as a conductive electrode for applying electricity to the adhesive. Application of 9 V for 1 min completely reduced the adhesive property of catechol functionalized adhesive. This is the first demonstration of using applied electricity to deactivate catechol-containing adhesive while it is still in direct contact with a surface. The ability to tune adhesion through *in situ* applied electricity provides another dimension in designing catechol containing smart adhesives.

3.2. Utilization of ROS Byproduct for Antipathogenic Applications. ROS is a broad-spectrum disinfectant.[3] Catechol-modified microgels were created with the ability to generate H_2O_2 (1−5 mM) over 4 days when hydrated.[16] These microgels rely solely on the autoxidation chemistry of catechol to convert molecular oxygen in solution into H_2O_2. The generated H_2O_2 was antimicrobial against both Gram positive (*Staphylococcus epidermidis*) and Gram negative (*Escherichia coli*) bacteria within 24 h of exposure. Additionally, these catechol-containing microgels decreased the infectivity of a nonenveloped virus, porcine parvovirus (PPV), and an enveloped virus, bovine viral diarrhea virus (BVDV), by 99.9% and 99.99%, respectively, within 12 h of incubation. By controlling the oxidation state of catechol, these microgels can be repeatedly activated (pH 7.4) and deactivated (pH 3.5) to generate antipathogenic levels of H_2O_2. These microgels do not contain the reactive ROS, and H_2O_2 is *in situ* generated by converting molecular oxygen in the aqueous solution through catechol oxidation. This simple activation process enables catechol-modified microgel to function as a lightweight and portable source of disinfectant.

H_2O_2 is not a very potent disinfectant.[3] To further enhance the antipathogenic property of catechol-modified microgels, these microgels were further modified with hematin (HEM), a porphyrin derivative that contains a ferric ion (Fe^{3+}) (Figure 4).[25] Fe^{3+} can convert the generated H_2O_2 to hydroxyl radical (•OH) via a Fenton-like reaction process. These microgels demonstrated faster and more effective antimicrobial activities against both *S. epidermidis* and *E. coli* cultured at starting concentrations of 10^6 and 10^7 CFU/mL, when compared with microgels that generated only H_2O_2. These microgels also reduced the infectivity of PPV and BVDV by 99.97% % and 99.997%, respectively. However, •OH alone did not provide sufficient antimicrobial property because of its short half-life (10^{-9} s). To overcome this issue, the microgels were further modified with a positively charged [2-(methacryloyloxy)ethyl] trimethylammonium chloride (METAC), which enhances the antibacterial performance of the microgel through electrostatic interactions between the positively charged microgels and the negatively charged pathogens.

Catechol generates $O_2^{\bullet-}$ in metal-ion-mediated oxidation, which can be further converted into $^1O_2$ by the metal ion.[19] Both $O_2^{\bullet-}$ and $^1O_2$ are more reactive when compared with H_2O_2.[3] When catechol-modified microgels were incubated in solutions containing up to 40 mM of various metal ions (e.g., Fe^{2+}, Ni^{2+}, Cu^{2+}, Co^{2+}, Pb^{2+}) more than 85% of these metal ions were removed from the solution.[19] Most interestingly, these metal ions were repurposed to generate ROS for organic dye degradation. Similarly, $^1O_2$ was produced by mixing catechol-modified microgel with iron magnetic nanoparticles (FeMNPs) instead of metal ions. This simple mixture completely degraded various types of azo-dyes within 24 h at pH ranging from 3 to 9. Additionally, the generated ROS degraded up to 90% of an antibiotic, ciprofloxacin, within 24 h and killed 99% of *E. coli* after 24 h of incubation. This simple

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mixture of catechol-modified microgel and FeMNP can potentially be utilized as a portable source for on-demand generation of ROS for bioremediation and water purification.

4. SUMMARY AND FUTURE OUTLOOK

In this Mini-Review, we focused on the oxidation chemistries of catechol as well as two relatively new applications that require tuning the oxidation states of catechol. Oxidation chemistry of catechol is critical to the curing and interfacial bonding of catechol-containing adhesives and coatings. Additionally, ROS is generated as a byproduct during the process of catechol oxidation. The ability to control the oxidation state of catechol provides a new approach for designing stimuli-responsive adhesive suitable for adhering to wet surfaces. ROS generation can be utilized to create portable biomaterials that can release the ROS on demand for antipathogenic applications and water purification.

Both pH-induced and electrochemical oxidation of catechol provided a basis for designing stimuli-responsive adhesive. However, an elevated level of voltage (9 V) was required to deactivate catechol, potentially because of the poor conductivity of the adhesive network.[24] This resulted in the electrolysis of water and is problematic when utilizing electrodes constructed using metals with reduced stability. It may be necessary to increase the conductivity of the adhesive network to reduce the need for elevated electrical potential. Additionally, a temporary protecting group such as a boronic acid[21] may be required to preserve the reversibility of the adhesive.

Using the byproduct of catechol oxidation for antipathogenic application is highly attractive. ROS is a popular disinfectant because of its biocompatible degradation products (i.e., water and oxygen).[3] Additionally, these catechol-containing biomaterials can be activated by simple hydration in an aqueous solution.[16,19,25] However, this technology has been only demonstrated to generate ROS when the catechol-containing materials were fully submerged in a solution, which may limit its applications. Specifically, the recent COVID-19 pandemic highlighted the need for antiviral materials that can disinfect surfaces that come into contact with a patient's respiratory droplets. A coating that can be activated by the moisture found within respiratory droplets to generate ROS has the potential to reduce the risk of indirect contact transmission. Additionally, a self-disinfecting coating can potentially be applied to reusable filters for respirators and face masks, which will provide added protection to the wearer. However, it may require a significantly higher rate of catechol oxidation to generate sufficient levels of ROS using limited levels of moisture found in respiratory droplets to engineer such a coating.

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Notes

The authors declare no competing financial interest.

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Bruce P. Lee is a Professor in the Department of Biomedical Engineering at Michigan Technological University. Prior to his current position, he cofounded a start-up company, Nerites Corporation, which aimed at commercializing tissue adhesive and coating inspired by mussel adhesive proteins. He was an awardee of the 2016 Office of Naval Research Young Investigator Program and the 2019 Bhakta Rath Research Award. His research is focused on applying mussel adhesive chemistry in designing bioadhesives, biomaterials, and stimuli-responsive materials.

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