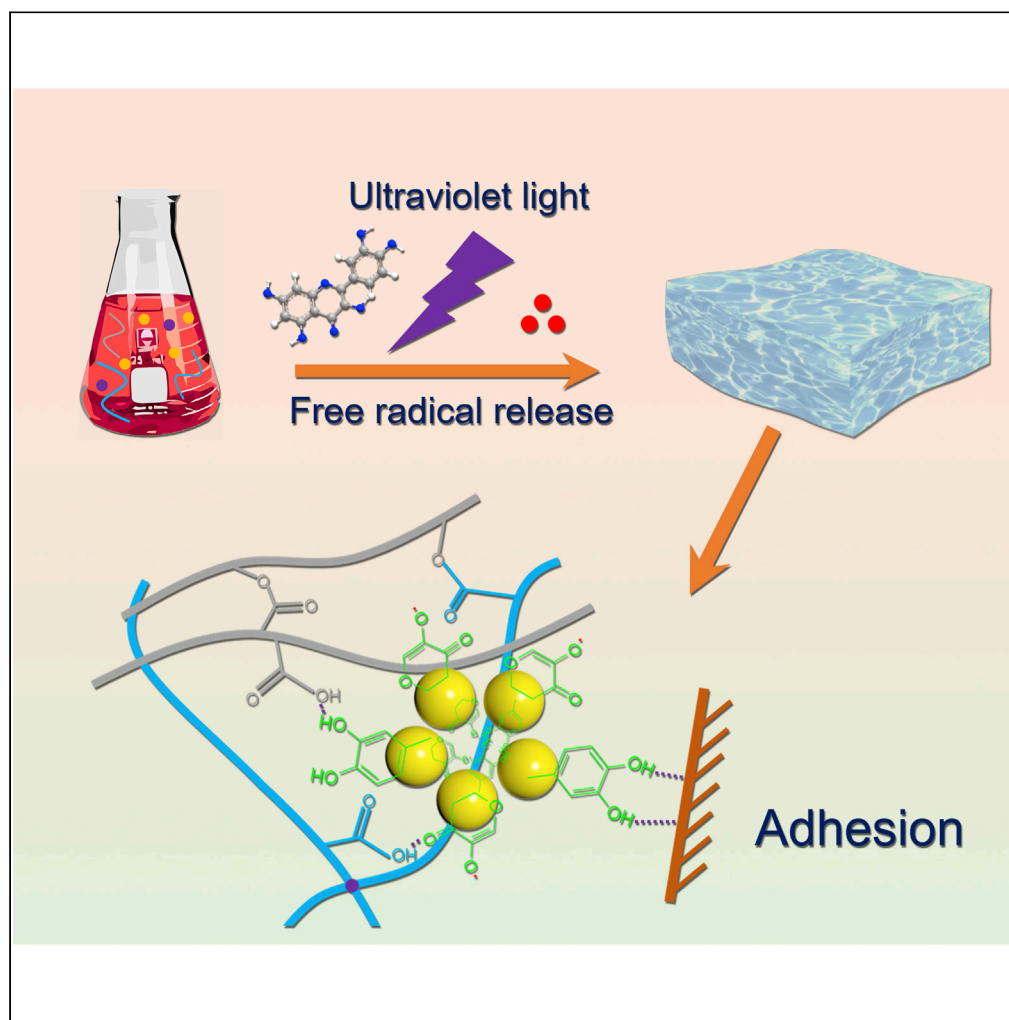## Article

Seeking Answers from Tradition: Facile Preparation of Durable Adhesive Hydrogel Using Natural Quercetin

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HIGHLIGHTS

Quercetin-assisted photoradical chemistry was developed for adhesive hydrogel

Quercetin composite hydrogel showed durable adhesion capacity

Quercetin composite hydrogel was used as electronic skin

Article

Seeking Answers from Tradition: Facile Preparation of Durable Adhesive Hydrogel Using Natural Quercetin

Daming Xiao,[1] Mingyue Jiang,[1] Xinyue Zhang,[1] Na Niu,[1] Jian Li,[1] Shouxin Liu,[1] Zhijun Chen,[1,2,*] and Shujun Li[1,*]

SUMMARY

Adhesive hydrogels containing catechol moieties have many important applications, but the fabrication of effective long-lasting adhesive hydrogels remains a challenge because of oxidative damage. Inspired by the traditional use of quercetin in ancient China, here, we have developed a novel method, based on quercetin-assisted photoradical chemistry, to fabricate a durable adhesive hydrogel, Q-hydrogel. In the presence of light, quercetin generates quinone/semiquinone radicals, which subsequently interact with ammonium persulfate (APS) to produce a large amount of free radicals and initiate polymerization of the hydrogel. As-prepared Q-hydrogel showed good mechanical and adhesive properties, which were attributed to the inherent structural advantages of quercetin. Because of the resistance of quercetin to oxidation, as-prepared Q-hydrogel also showed good adhesive properties even after treatment with oxidizing agents. Capitalizing on its conductivity and adhesive properties, Q-hydrogel was successfully used to produce wearable sensors capable of detecting human motion.

INTRODUCTION

Adhesive hydrogels have huge potential in a variety of areas, including bio-medical care and electronic skins (Gan et al., 2019a, 2019b; Liao et al., 2019; Lei et al., 2017; Ma et al., 2019; Wang et al., 2018; Wirthl et al., 2017; Li et al., 2018; Xu et al., 2019). Different design strategies, including those based on two-layer adhesive surface-dissipative matrices (Chen et al., 2015; Wu et al., 2018; Yang et al., 2016; Zhang et al., 2016), nucleobase tackifying (Gao et al., 2019; Liu et al., 2017, 2019a, 2019b), and well-patterned structures (Jin et al., 2017; Mredha et al., 2018; Zhao et al., 2017) have been used to develop adhesive hydrogels. Recently, mussel-inspired polydopamine-based adhesive hydrogels have been shown to have especially good performance because of their strong cohesive and adsorptive properties (Gao et al., 2013; Han et al., 2017a, 2017b, 2017c; Tang et al., 2019). Building on these studies, many catechol moiety-incorporating compounds have been used to develop adhesive hydrogels (Lee and Konst, 2014; Li et al., 2015; Narkar et al., 2016). Because catechol functional groups can form covalent/non-covalent bonds with different materials (Saiz-Poseu et al., 2019; Wang et al., 2019), these hydrogels can adhere repeatedly well to a variety of surfaces (Gan et al., 2019a, 2019b; Han et al., 2017a, 2017b, 2017c; Lee et al., 2007). Although much progress has been made in this area, the adhesive properties of most hydrogels are destroyed by oxidation (Jing et al., 2018; Maier et al., 2018; Maier and Butler, 2017; Kord Forooshani and Lee, 2017). It is, therefore, important to develop long-lasting adhesive hydrogels that are resistant to oxidation. Quercetin, a flavonoid with catechol functionality that is easily extracted from the flower buds of *Sophora japonica* L. (He et al., 2018a, 2018b), was widely used to produce royal dyes and herbal medicines in ancient China. Additionally, Schmidt et al. reported that they used catechol moiety-incorporating plant phenols together with zein protein for preparing a sustainable and high-strength adhesive (Schmidt et al., 2018). Inspired by this, here, we have focused on quercetin, which binds strongly to guest materials and has good antioxidative capacity, to develop an oxidation-resistant, high-performance adhesive hydrogel. This is the first report to describe the use of quercetin-assisted radical chemistry to prepare an adhesive hydrogel (Q-hydrogel) with good antioxidative capacity upon light irradiation in the presence (Figure 1). Upon light irradiation, quercetin generates quinone/semiquinone radicals, which subsequently interact with APS to produce a large amount of free radicals and initiate polymerization of the hydrogel. As-prepared Q-hydrogel had good mechanical properties and, because of the high antioxidative capacity of quercetin, also showed
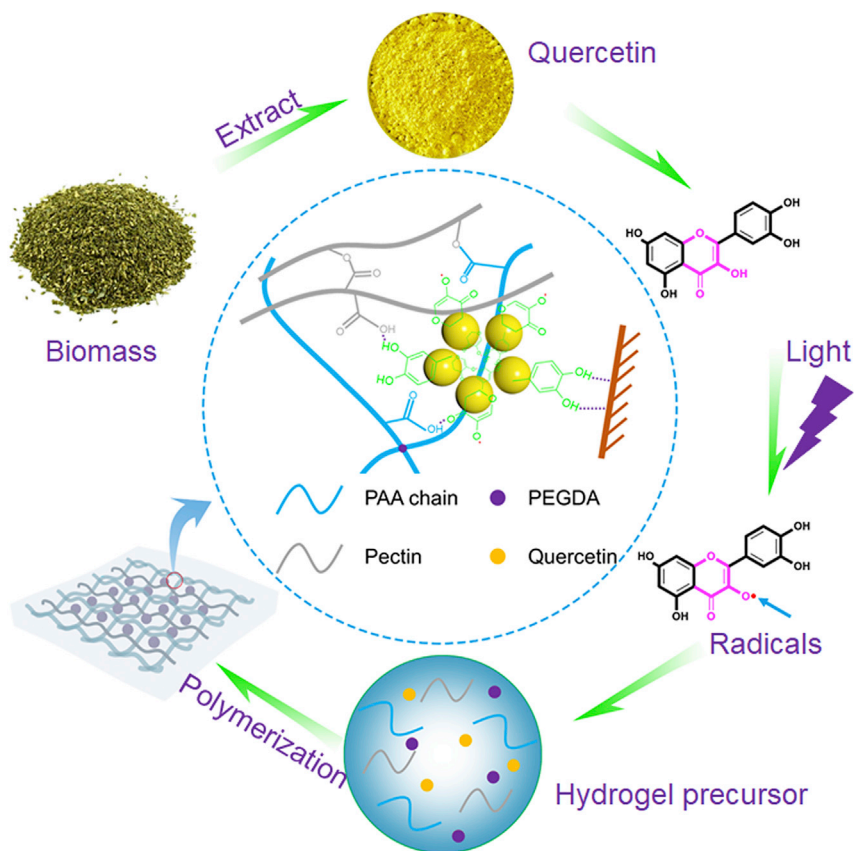
Figure 1. Schematic Illustration of Quercetin-Assisted Radical Chemistry Triggered for Preparation of Q-hydrogel upon Light Irradiation

long-lasting adhesion, even after treatment with strong oxidizing agents. As demonstrations of potential applications, Q-hydrogel was incorporated into a textile and used to prepare a wireless wearable sensor capable of detecting human motion.

RESULTS

Quercetin-Assisted Radical Chemistry for Preparing Q-hydrogel

First, we investigated quercetin-assisted radical chemistry. The mechanism of free radical generation was studied using electron spin-resonance spectroscopy (ESR). Quercetin showed maximum absorbance at ~390 nm (Figure S1) and quercetin-assisted radical chemistry was, therefore, investigated using 375 nm light as the irradiation source. Upon light irradiation, the ESR spectrum of a quercetin/APS showed a signal with a g value of 2.0039, which was attributed to quinone/semiquinone radicals (Figure 2A). The ESR spectrum of the quercetin/APS in the dark showed the same peak, but with much lower intensity, indicating that the quantity of quinone/semiquinone radicals was much smaller (Figure 2A). Pure APS showed a very weak signal in the ESR spectrum upon light irradiation (Figure S2). ESR spectra of the quercetin/APS were also recorded after irradiation for different periods of time. Longer exposure of the quercetin/APS to UV light produced more radicals (Figure 2B). These results demonstrate that APS alone generates few radicals upon light irradiation, whereas a solution of quercetin/APS generates many more radicals under the same conditions, making it possible to polymerize the monomer and cross-linker to form an adhesive hydrogel. Having characterized quercetin-assisted radical chemistry, this was then used to prepare Q-hydrogels. Acrylic acid (AA) monomers, APS, polyethylene glycol diacrylate (PEGDA), and pectin were mixed with suspensions containing different amounts of quercetin (Table S1). Under irradiation with 375 nm light, hydrogels were formed by quercetin-assisted radical chemistry (Figures 2C and 2D). In a control experiment, no hydrogel was formed when the same formulation, but without quercetin, was irradiated under the same conditions (Figure S3). The suspensions containing quercetin also did not form hydrogels without light
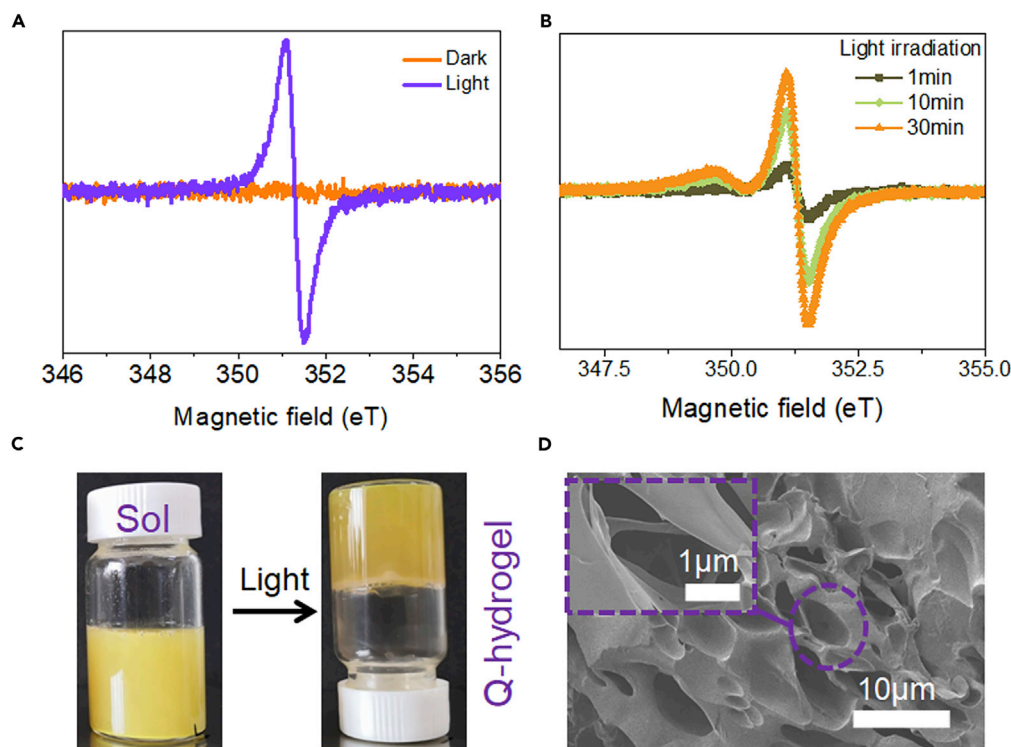
Figure 2. Quercetin-Assisted Photoradical Gelation
(A) ESR spectra of quercetin/APS upon light irradiation and in the dark.
(B) ESR spectra of quercetin/APS after light irradiation for different lengths of time.
(C) Q-hydrogel precursor suspension of quercetin/APS in dark environment (left) and after UV irradiation (right).
(D) SEM images of as-formed Q-hydrogel to the condition mentioned in Figure 2C; scale bar, 10μm. Inset: Magnified SEM images of as-formed Q-hydrogel; scale bar, 1 μm.

irradiation (Figure S3). Quercetin-assisted radical chemistry can also initiate the polymerization of other free-radical monomers, such as acrylamide, suggesting that the as-developed quercetin-assisted radical chemistry is generally applicable and can be used to prepare a variety of hydrogels (Figure S4).

Mechanical Properties of Q-hydrogels

The Q-hydrogels were resilient, stretchable, and tough. Typical tensile stress-strain curves of the hydrogels were investigated and tensile strain was found to reach a maximum value of 1,800% when the amount of quercetin in the hydrogel was 0.35 wt % (Table S1). To understand why 0.35 wt % sample showed the best performance, the polymerization behavior of acrylic acid in the presence of 0.31%, 0.35%, and 0.56% quercetin was studied, since the molecular weight strongly influenced their mechanical properties. Interestingly, GPC trace only showed one main peak for polyacrylic acid formed in the presence of 0.31% and 0.56% quercetin. Mn of polyacrylic acid formed in the presence of 0.31% and 0.56% were ~160,000 and 420,000, respectively (Figure S5), whereas there were two peaks in GPC trace of polyacrylic acid formed in the presence of 0.35%. Mn of these polyacrylic acid formed in the presence of 0.35% quercetin were ~180,000 and 17,000, respectively (Figure S5). The difference explained the best performance of the hydro-gel triggered by 0.35% quercetin. It is clear that one common strategy to develop a tough hydrogel is to interpenetrate polymer networks with relatively short and long polymer chains. Under deformation, the short-chain networks can be fractured and/or physically de-cross-linked to dissipate mechanical energy, whereas the long-chain networks will maintain the high elasticity of the hydrogels (Zhao, 2014). For further comparison, poly(acrylic acid) hydrogel (PAA hydrogel) and the pectin/poly(acrylic acid) hydrogel (P-PAA hydrogel) were prepared assisted by radical chemistry in the presence of heating (supporting information). Q-hydrogel showed values much higher than the values for PAA hydrogel (~250%) and P-PAA hydrogel (~500%) (Figure 3A). The addition of ~0.35 wt % of quercetin also produced a hydrogel with the highest tensile strain value (Figure 3B). Load-unload tensile stress-strain curves of the Q-hydrogel containing
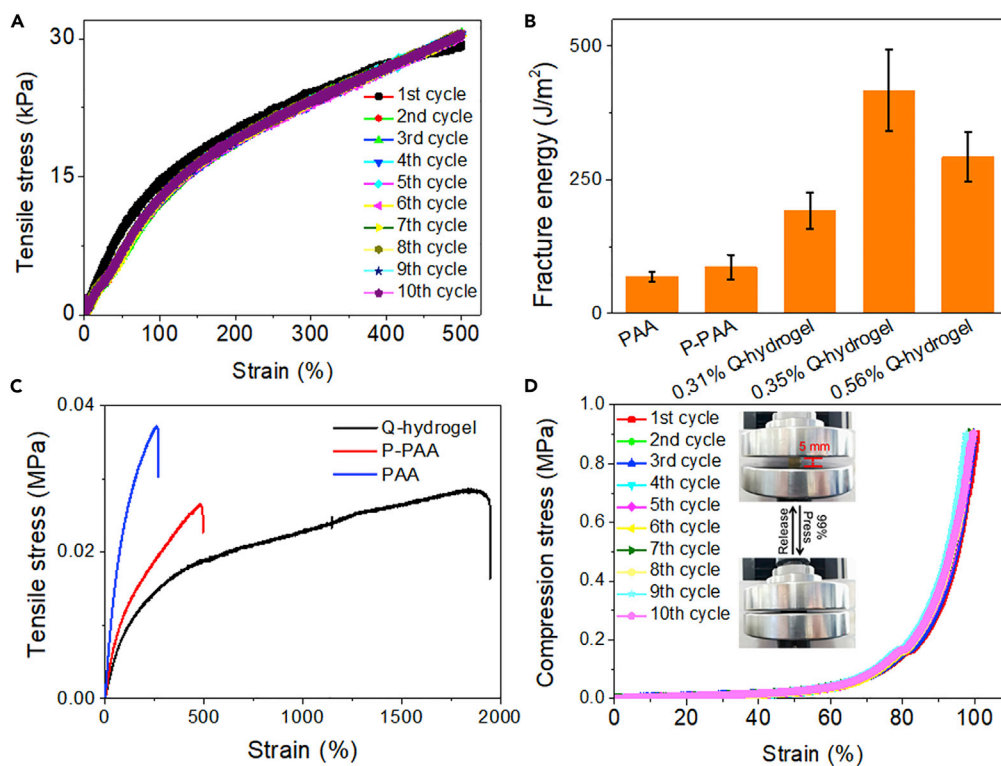
Figure 3. Mechanical Properties of Hydrogel
(A) Tensile loading-unloading curves of Q-hydrogel.
(B) Fracture energy of hydrogels containing different amounts of quercetin.
(C) Typical tensile stress-strain curves of hydrogels.
(D) Recovery of Q-hydrogel after removal of compressive load occurred within 2 min.

0.35 wt % were then constructed. The load-unload tensile stress-strain curves showed excellent reproducibility over ten cycles (Figure 3C). The Q-hydrogel was able to withstand high compression to complete deformation without breaking and, after the compressive load was removed, the hydrogel recovered automatically and rapidly to its initial shape, even after ten cycles (Figure 3D). The load-unload compression stress-strain curves indicated that the Q-hydrogel has good recoverability. The good mechanical properties of the hydrogel are attributed to three factors. First, pectin interpenetrates the PAA networks and strengthens the hydrogel. Second, pectin contains a large number of -OH and -COOH groups, which are important active sites of hydrogen bonds in the noncovalent interaction with acrylic acid and quercetin (Servais et al., 2008). Thus, quercetin, PAA, and pectin form noncovalent interactions, which dissipate energy under large deformation and improve the mechanical properties of the hydrogel. Third, quercetin has many hydrophilic hydroxyl groups and can, therefore, form hydrogen bonds within the hydrogel network and thus improve its mechanical properties. Because of its superior mechanical properties, the Q-hydrogel containing 0.35 wt % quercetin was used in all subsequent tests.

Adhesive Properties

The adhesive properties of Q-hydrogel were systematically investigated. Q-hydrogel can adhere to both hydrophilic and hydrophobic surfaces, such as glass, wood, rubber, polytetrafluoroethylene, and tissue (pork skin) (Figure 4A). The adhesive strength of Q-hydrogel on pork skin was quantified using a tensile adhesion test and found to be $\sim$110 J/m^2 (Figure 4B). Notably, the nice adhesive properties might also be partially contributed by catechol-protein interaction (Schmidt et al., 2018). Q-hydrogel maintained good adhesion to pork skin even after 50 peeling/adhering cycles and showed similar good adhesive properties on the author's skin (Figure 4C). Typically, adhesive hydrogels incorporating catechol moieties lose their adhesive properties in strongly oxidizing environments because of overoxidation of the catechol moieties. The resistance of Q-hydrogel to oxidation was assessed by treating the hydrogel with different concentrations of H$_2$O$_2$ (for 30 min). Surprisingly, Q-hydrogel maintained good adhesion to pork skin after
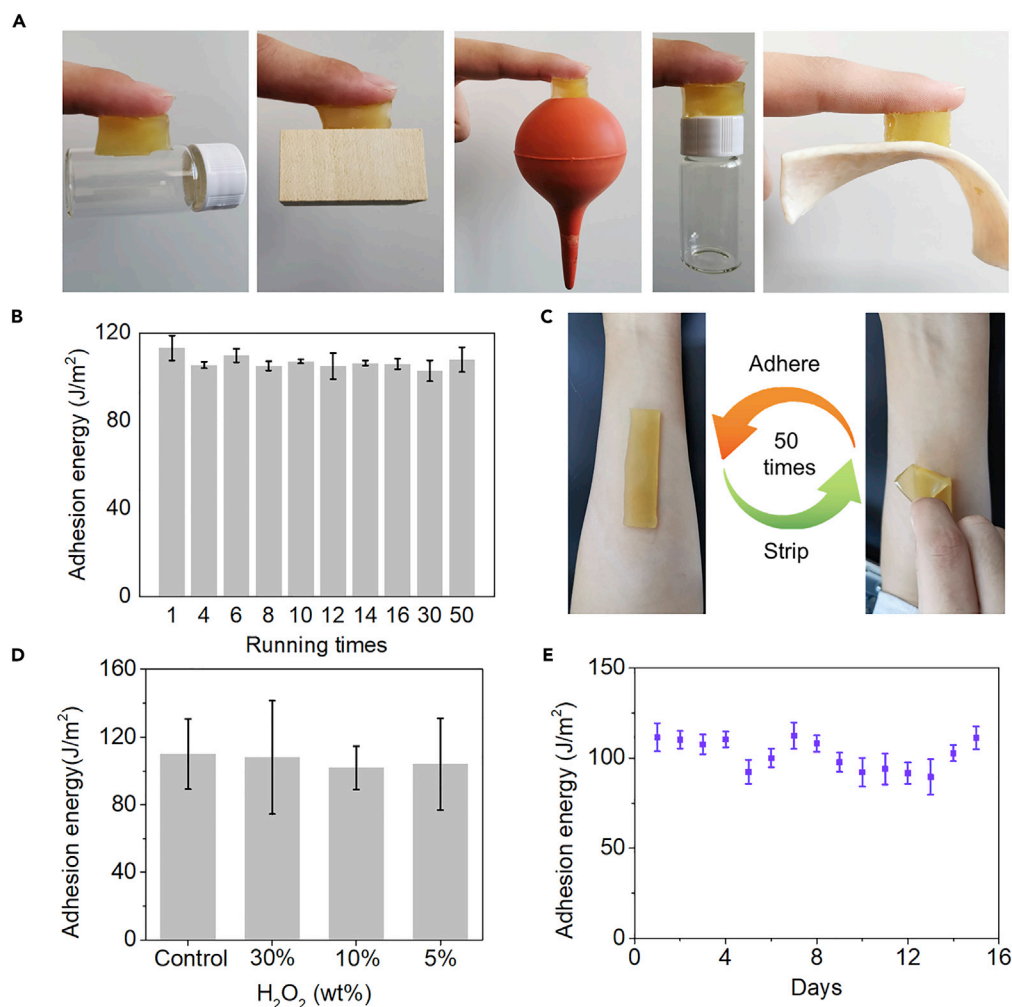
Figure 4. Adhesive Properties of Q-hydrogel

(A) Q-hydrogel sticking to different surfaces.

(B) Adhesive strength of Q-hydrogel on pork skin after 50 cycles of adhesion-peeling.

(C) Repeated adhesion-peeling of Q-hydrogel on author's skin. No residue or irritation of the skin was found after 50 cycles of adhesion-peeling.

(D) Adhesion energy of Q-hydrogel/pork skin after treatment of Q-hydrogel with different concentrations of H_2O_2 (error bar means the standard deviation).

(E) Adhesion energy of Q-hydrogel/porcine skin after different storage times. The hydrogel was stored in a sealed environment at room temperature (21°C).

treatment with this strong oxidant (Figure 4D). The continued adhesiveness of Q-hydrogel might be attributable to the way in which quercetin reacts with oxidants (Jing et al., 2018; Maier et al., 2018; Maier and Butler, 2017). Specifically, although part of the catechol structure was oxidized by H_2O_2, which reduced the adhesive strength, chemical oxidation opened the lactone ring of quercetin to generate a series of carboxylic acid and hydroxyl moieties and enhanced the adhesive properties, instead (Scheme S1) (Nimse and Pal, 2015; Osman et al., 2008). Generally, the enhanced adhesive strength might compromise the reduced one. That is the reason for the minor decrease for adhesive performance of Q-hydrogel after oxidation. Encouraged by this result, we further investigated the long-term adhesive properties of Q-hydrogel and found that its adhesive strength was not reduced after storing for 15 days (Figure 4E).

Wearable Sensors for Monitoring Human Motion

Polyacrylic acid network in Q-hydrogel provided proton carriers and enabled it conductive (Moharram et al., 1998; Rhim et al., 2005). Therefore, the possibility of using Q-hydrogel in a wearable electronic device
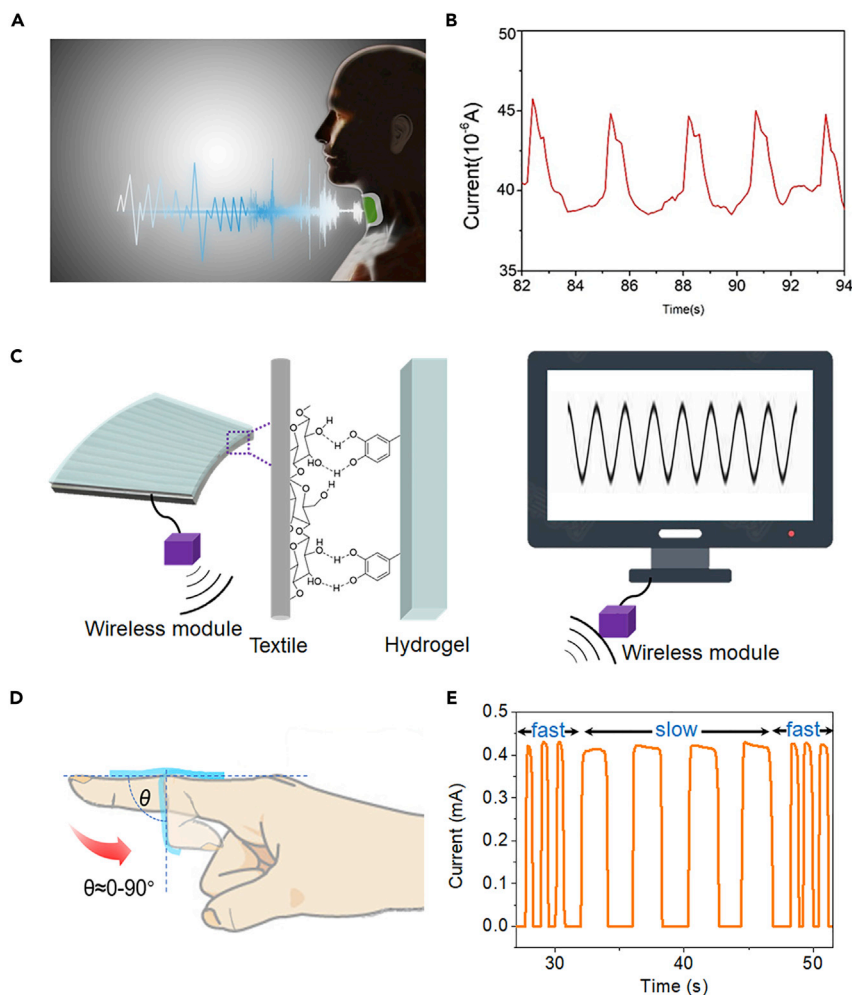
Figure 5. Performance of Wearable Q-hydrogel Sensor
(A) Schematic illustration of sensing man's throat during cyclic swallowing using Q-hydrogel.
(B) Current response curve of a sensor attached to a man's throat during cyclic swallowing.
(C) Schematic illustration of wireless setup developed for sensing motion.
(D) Illustration of cyclic bending and recovery of wireless wearable sensor on finger.
(E) Current response curve of sensor upon periodical bending motion with different speeds.

or as an electronic skin was investigated next. The electrical characteristics of Q-hydrogel were measured using a CHI 660e electrochemical workstation as described in Supplemental Note 3. Q-hydrogel shows good conductivity and, in preliminary experiments, its sensitivity to touch and bending were investigated (Figure S6). Q-hydrogel showed a good response to mechanical stimulation at different speeds (Figures S7 and S8). Q-hydrogel was next used to sense swallowing motion by spreading the sensor over the Adam's apple of a male volunteer (Figure 5A). In the initial state, the sensor was taut and the current was small. Swallowing caused an upward movement of the Adam's apple, which released the tension in the sensor, leading to a larger current. Marked variations in the strength of the current were thus caused by swallowing (Figure 5B). Encouraged by these results, which show that Q-hydrogel is very sensitive to distortion, the adhesive hydrogel was next used to prepare a wearable wireless conductive textile (Figure S9). Q-hydrogel, which was prepared *in situ* in the fabric, adhered very well to the textile because of the presence of quercetin moieties. After intensive twisting, the conductivity of the textile did not noticeably change, showing that the hydrogel was stably incorporated into the textile (Figure S10). As-prepared textile was then coupled to a home-made setup to fabricate a wireless wearable sensor, which was used to sense bending motion (Figures 5C and S11). As-obtained textile was attached to the index finger to detect the bending motion of the second joint (0°–90°) (Figure 5D and Video S1). The strength of the current showed a regular

variation with the angle of the finger joint (Figure 5E). The changes in current intensity could, in the future, be used to record swallowing, or other motions, of patients.

DISCUSSION

In summary, inspired by the traditional uses of quercetin, we have developed an efficient adhesive Q-hydrogel using quercetin-assisted radical chemistry. As-prepared Q-hydrogel has a number of advantages. First, Q-hydrogel shows long-lasting adhesiveness, which is attributed to the resistance of quercetin to oxidation. Second, the hydrogel adheres well to textiles, has good conductive properties. and is easily prepared under mild conditions. Q-hydrogel could thus be prepared *in situ* within textiles to produce wearable sensors. Since many naturally occurring phenolic compounds contain catechol moieties, our work may inspire others to use these natural phenolic compounds to construct other durable adhesive hydrogels.

Limitation of the Study

We have developed a durable adhesive hydrogel using quercetin. However, the gelation of hydrogel required about 30-min UV irradiation. This long irradiation time and short wavelength might hinder its future applications *in vivo*. However, the long irradiation time might be shortened by adding N,N,N',N'-tetramethylethylenediamine as catalyst. Additionally, sodium periodate should be used for further evaluating the susceptibility of the Q-hydrogel to be oxidized.

Resource Availability

Lead Contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Zhijun Chen (Chenzhijun@nefu.edu.cn).

Materials Availability

This study did not generate new unique reagents.

Data and Code Availability

This study did not generate/analyze datasets/code.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2020.101342.

AUTHOR CONTRIBUTIONS

Z.C. and S.L. participated in the conception and design of the research. D.X. carried out the experiments and characterizations. Z.C., D.X., and M.J. prepared the figures and drafted the manuscript. X.Z., J.L., N.N., and S.L. revised the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Supplemental Information

Seeking Answers from Tradition: Facile

Preparation of Durable Adhesive

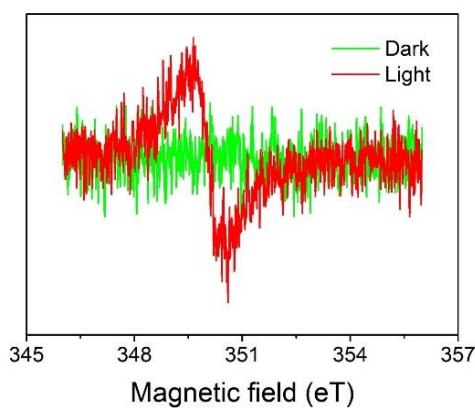# Hydrogel Using Natural Quercetin

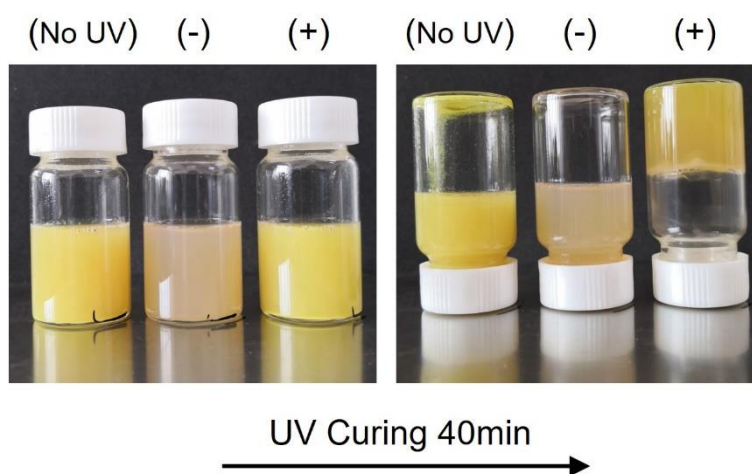Daming Xiao, Mingyue Jiang, Xinyue Zhang, Na Niu, Jian Li, Shouxin Liu, Zhijun Chen, and Shujun Li

Supplemental Information
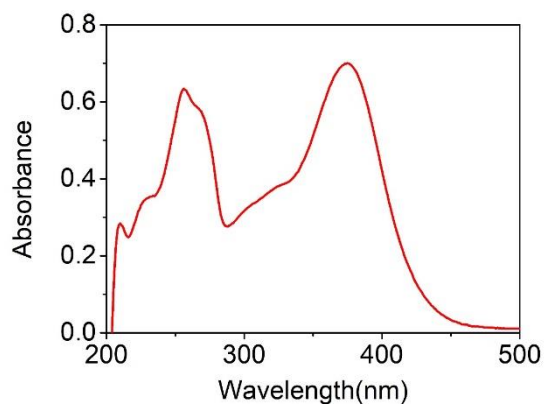
Figure S1. Related to Figure 2. Ultraviolet absorption spectrum of quercetin (0.1 mg/mL in ethanol).

Figure S2. Related to Figure 2. ESR spectra of APS upon light irradiation and in the dark.

UV Curing 40min

Figure S3. Related to Figure 2. Precursor suspensions after curing under UV light (375 nm) for 40 min. Left, no irradiation; Center, without quercetin; Right, with quercetin.
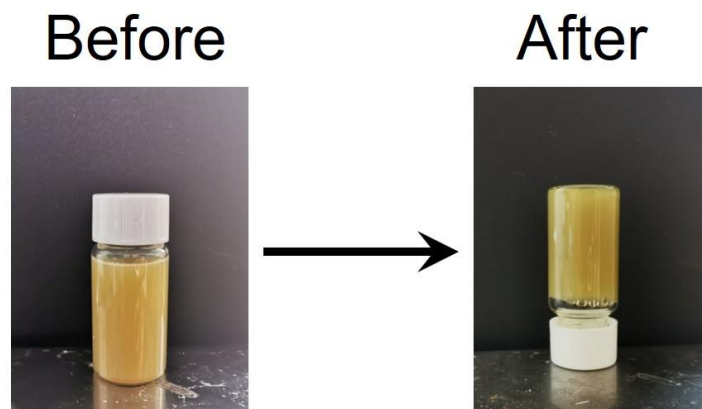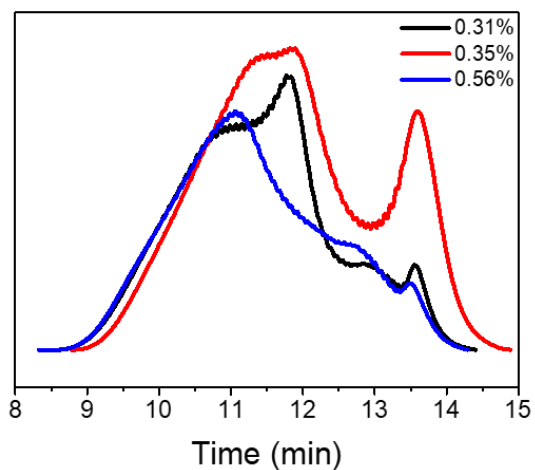
Figure S4. Related to Figure 2. P-PAM (Quercetin-doped polyacrylamide hydrogel) gel formed by curing under UV light (375nm) for 30 min.

Table S1. Related to Figure 3. Composition of different hydrogels.

| Hydrogel	AA [mL]	Pectin/ AA [wt %]	APS/ AA [wt %]	PEGDA/ AA [wt %]	Quercetin [mg]	Deionized Water [mL]	Water Content [wt %]
PAA Hydrogel[a]	2.7	0	5	0.1	0	10	79
P-PAA Hydrogel[a]	2.7	10	5	0.1	0	10	77
0.31% Q-Hydrogel[b]	2.7	10	5	0.1	9	10	77
0.35% Q-Hydrogel[b]	2.7	10	5	0.1	10	10	77
0.55% Q-Hydrogel[b]	2.7	10	5	0.1	16	10	77

[a] Heating for 40 min at 60 °C; [b] Irradiation (375 nm) for 40 min.

Figure S5. Related to Figure 3. GPC traces of polymerized acrylic acid (PAA) in the presence of 0.31%, 0.35% and 0.56% quercetin. (For the PAA formed in the presence of 0.31% quercetin, D = 5.49; For the PAA formed in the presence of 0.35% quercetin, D = 7.25; For the PAA formed in the presence of 0.56% quercetin, D = 5.74).
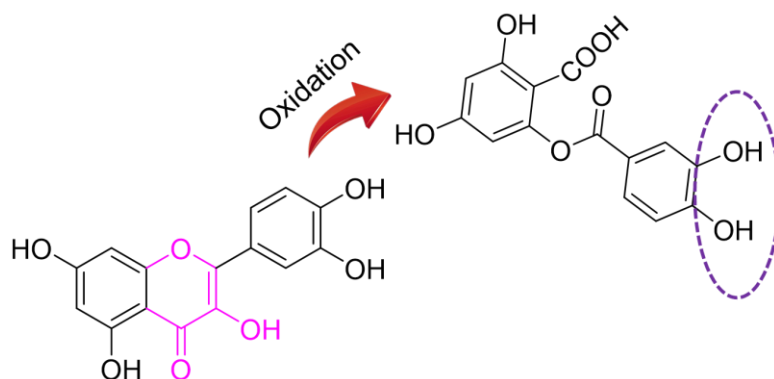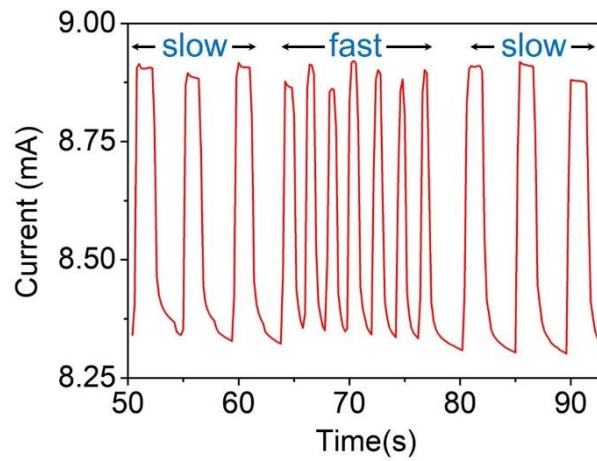

**Scheme S1. Related to Figure 4**. Oxidation of quercetin.
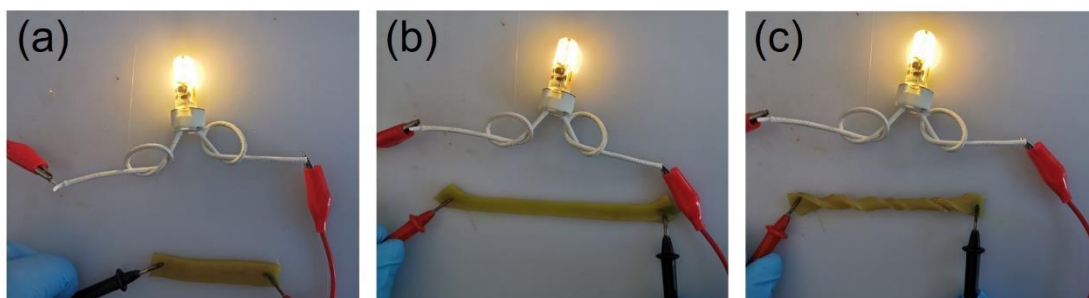
Figure S6. Related to Figure 5. Different shape characteristics of electronic sensor cause bulb to glow. (a) Normal state; (b) Stretched state; (c) Distorted and stretched state.
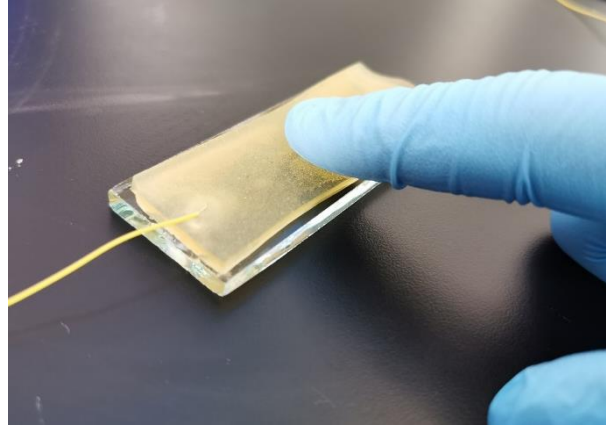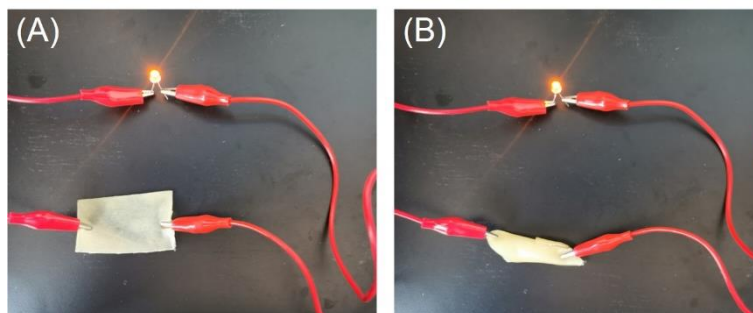
Figure S7. Related to Figure 5. Photograph of finger pressure-sensing device prepared using Q-hydrogel.
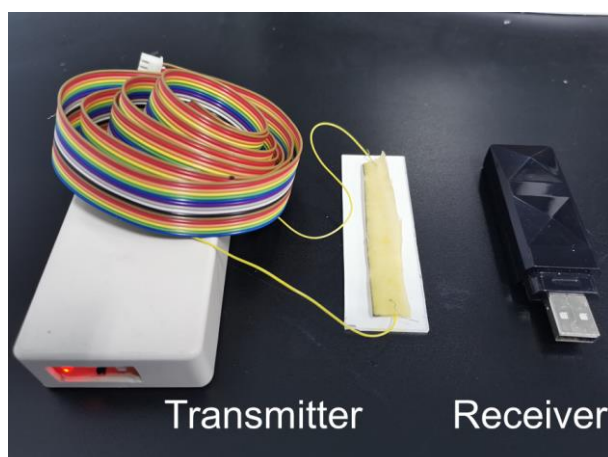

Figure S8. Related to Figure 5. Real time-current response to pressure applied at different speeds.
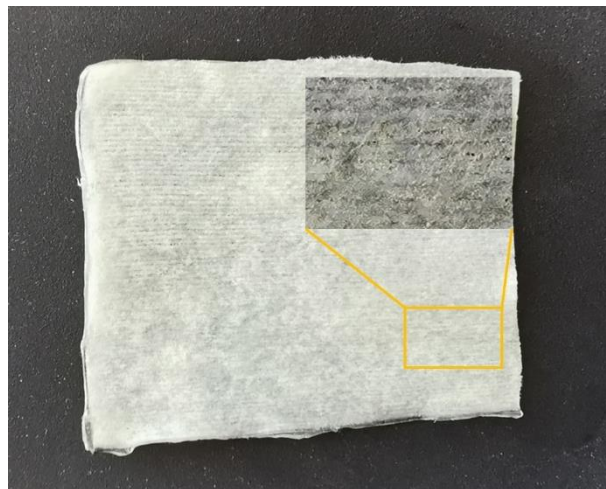
Figure S9. Related to Figure 5. Photograph of conductive wearable fabric (electronic skin).

Figure S10. Related to Figure 5. .Demonstration of electrical conductivity of electronic skin under different conditions. a) In original state; (B) After twisting and pulling.

Figure S11. Related to Figure 5. Photographs of wireless wearable sensor system. a) Wireless mechanical sensing device. Inset shows wireless receiver; b) Pressure device.

Video S1. **Related to Figure 5**. Video of sensing the finger bending motion.

Transparent Methods

Materials

All purchased reagents and solvents were used without further purification. All solvents were analytical reagent grade. Pectin (P, galacturonic acid content ≥ 74%), AA (99.0%) and quercetin (95%) were purchased from Aladdin (Shanghai, China). APS (98.0%) was purchased from Merck (Shanghai, China). Poly (ethylene glycol) dimethacrylate (PEGDA, average Mn = 700) was purchased from Macklin (Shanghai, China). Deionized water was used in the experiments.

Experimental Section

Characterization

ESR spectra were recorded at 9.852 GHz using an A300 ESR Spectrometer (Bruker, Germany) by Testdog Company (Chengdu, China). Morphological structures were examined using a JSM 7500F scanning electron microscope (JEOL, Japan). Mechanical and adhesive properties of the hydrogels were measured using a UTM2203 universal testing machine (Shenzhen SUNS

Technology Stock Co. Ltd., Shenzhen, China), with a 100 N load cell. Details are provided in Supplementary Notes 1 and 2. Electrochemical performance was tested using a CHI660e electrochemical workstation (Chenhua, Shanghai, China). The relative number-average molecular weights were determined at 35 °C by gel permeation chromatography (GPC, Shimadzu Rid-20A) equipped with a refractive index detector (Shimadzu RID-20) and the eluent at 0.6 mL/min. The calibration was built on polyethylene glycol standards. The mobile phase was 0.1M $NaNO_3$ and 0.06% NaN_3.

Preparation of Q-hydrogel
Homogeneous suspensions were prepared by stirring AA, pectin, APS and PEGDA with different amounts of quercetin in deionized water. The solutions were then injected into sealed reaction molds and irradiated at 375 nm for 40 min at room temperature using an LED UV lamp to obtain Q-hydrogels. The formulation of the hydrogels is denoted as x QC-P-PAA, where x is the mass of quercetin. Full details of preparation and composition of the various hydrogels are listed in Supplementary Table S1.

Preparation of PAA hydrogel
AA, PEGDA, APS and deionized water were stirred to prepare a homogeneous suspensions. The solution was injected into a sealed reaction mold and heated at 60°C for 40 min to obtain PAA hydrogel.

Preparation of P-PAA hydrogel
AA, PEGDA, APS and deionized water were stirred to prepare a homogeneous solution. The solution was injected into a sealed reaction mold and heated to 60°C for 40 min to obtain P-PAA hydrogel.

Fabrication and electrochemical testing of flexible conductive wearable fabric
A uniformly mixed solution of quercetin and P-PAA was coated onto a nonwoven fabric. The coated fabric was placed in a mold, cured under ultraviolet light for 40 min, and then peeled from the mold to obtain the Q-hydrogel sensor.

Supplemental Notes

Supplemental Note 1: Mechanical property testing
The hydrogels were molded into cylindrical specimens (D = 15 mm, H = 10 mm) for compression testing and into rectangular specimens (L = 5 mm, W = 25 mm) for tensile testing. Measurement of mechanical and adhesiveness properties of the hydrogels were carried out using a universal testing machine (UTM2203, SUNS TEST, China) with a 100 N load cell. The compressive tests were carried out at a speed of 1 mm min^{-1}, with a compression of 99 %. The tensile strength test of the hydrogel was performed at an extension speed of 50 mm min^{-1}. The fracture energy was tested using a classical single-edge notch test, as previously described. (Gan et al.,2018)
Supplemental Note 2: Adhesion tests

A 180° peeling test was used to measure the adhesion energy of Q-hydrogel and skin bonding. The Q-hydrogel samples were 70 mm in length, 20 mm in width and 2 mm in thickness. The free ends of the samples were fixed to the chuck of a tensile testing machine with a 100 N load cell. The peeling rate was fixed at 50 mm min^{-1}.

Supplemental Note 3: Wireless mechanical sensing test

Time-current curves were obtained using a CHI 660e electrochemical workstation. Pressure was applied and released by loading or unloading different speeds onto the sensor, and a time-current curve that can response to different compression speeds was obtained in real time. Q-hydrogel was also tested as an electronic skin. Firstly, the hydrogel was stuck on a finger. Secondly, the hydrogel was stuck onto the neck of a male volunteer and, interestingly, time-current curves were produced in real time by swallowing. Finally, a conductive fabric, or electronic skin, was prepared *in situ* in the textile and connected to a wireless transmission device to produce a wearable wireless sensor that is able to monitor finger bending at different bending speeds in real time.

Supplemental References

Gan, D., Han, L., Wang, M., Xing, W., Xu, T., Zhang, H., Wang, K., Fang, L., and Lu, X. (2018). Conductive and Tough Hydrogels Based on Biopolymer Molecular Templates for Controlling in Situ Formation of Polypyrrole Nanorods. ACS Appl. Mater. Interfaces. *10,* 36218-36228.