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Development of functional biointerfaces by surface modification of polydimethylsiloxane with bioactive chlorogenic acid

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ABSTRACT

The effect of physicochemical surface properties and chemical structure on the attachment and viability of bacteria and mammalian cells has been extensively studied for the development of biologically relevant applications. In this study, we report a new approach that uses chlorogenic acid (CA) to modify the surface wettability, anti-bacterial activity and cell adhesion properties of polydimethylsiloxane (PDMS). The chemical structure of the surface was obtained by X-ray photoelectron spectroscopy (XPS), the roughness was measured by atomic force microscopy (AFM), and the water contact angle was evaluated for PDMS substrates both before and after CA modification. Molecular modelling showed that the modification was predominately driven by van der Waals and electrostatic interactions. The exposed quinic-acid moiety improved the hydrophilicity of CA-modified PDMS substrates. The adhesion and viability of *E. coli* and HeLa cells were investigated using fluorescence and phase contrast microscopy. Few viable bacterial cells were found on CA-coated PDMS surfaces compared with unmodified PDMS surfaces. Moreover, HeLa cells exhibited enhanced adhesion and increased spreading on the modified PDMS surface. Thus, CA-coated PDMS surfaces reduced the ratio of viable bacterial cells and increased the adhesion of HeLa cells. These results contribute to the purposeful design of anti-bacterial surfaces for medical device use.

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1. Introduction

Bacteria-free devices are universally important for numerous applications that improve human health, such as tissue engineered materials [1], biomedical devices and biosensors. Device-related infections (DRIs), which arise from the adhesion and proliferation of bacteria on the surfaces of biomedical devices and implants, are the significant concern in implant surgery [2]. Thus, the design and fabrication of novel nanostructured surfaces that mitigate bacterial colonisation or inhibit bacterial growth is required to improve current medical devices. Most existing anti-bacterial agents are natural compounds that have been either extracted from microorganisms, such as penicillin, streptomycin and β-lactams [3] or chemically modified. However, the emergence of antibiotic-resistant bacteria is becoming an increasingly serious problem with the abuse of anti-bacterial drugs.

One prominent example is the recent discovery of a metallo-β-lactamase (MBL) named NDM-1 (New Delhi metallo-β-lactamase), which was identified from *Klebsiella pneumoniae* (strain 05-506) and *Escherichia coli* isolates [4]. Most isolates with the NDM-1 enzyme are resistant to standard intravenous antibiotics [5]. Thus, because of the disadvantages of conventional antimicrobial agents, the development of novel antimicrobial agents has gained considerable attention. For example, Sumitha et al. incorporated silver nanoparticles into poly (ε-caprolactone) (PCL) scaffolds during the process of electrospinning [1]. Eby et al. reported a method to synthesise antimicrobial medical instruments by coating them with silver nanoparticles [6]. "Nanosilver" has been introduced into some consumer products [7] and silver-containing textiles are being advertised for their anti-bacterial effect [8]. Although nanoparticles (NPs) were originally considered nontoxic materials, an increasing number of studies report toxicity associated with NP exposure [9–11]. Therefore, other biocompatible agents should be investigated and developed.

Chlorogenic acid (CA), the ester of cinnamic and quinic acid, is the most abundant hydroxycinnamic acid found in food. Additionally, it is nontoxic [12] and has been shown to inhibit bacterial growth [13]. We used CA to modify the surface of polydimethylsiloxane (PDMS) substrates. PDMS elastomer is of particular interest because it is flexible, easily moulded, nontoxic, optically transparent, gas permeable, inexpensive and chemically inert [14]. Because of these merits, considerable effort has been focused on using PDMS in many applications, such as the development of

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antimicrobial materials. Komaromy et al. investigated the effect of changes to the physical properties of PDMS on the attachment and viability of bacterial cells [15]. Goyal et al. demonstrated a method for embedding noble metal NPs in free standing PDMS composite films to synthesise a material with enhanced anti-bacterial properties [16]. Although PDMS has many advantages, its hydrophobic surface restricts its widespread application. Therefore, various solutions have been proposed to improve the hydrophilicity of PDMS surfaces, including plasma oxidation [17], ultraviolet irradiation and adsorbed coatings [18,19]. Although these methods have allowed the tailoring of PDMS surface properties, challenges still remain, including reduced biocompatibility after chemical treatment, hydrophobic recovery and physical damage to the PDMS surface [20,21].

Here, we report a simple approach to modify PDMS with CA (Scheme 1). Our experimental results demonstrate the development of a bi-functional, CA-modified PDMS substrate with increased antimicrobial properties that supports cell growth. These anti-bacterial biomedical devices locally inhibit the growth of bacteria and are not toxic to the surrounding tissue.

2. Materials and methods

2.1. Materials

CA was purchased from Nanjing Zelang Medical Technology Co. Ltd. PDMS elastomer (Sylgard® 184 silicone elastomer kit) was obtained from Dow Corning Corporation (Midland, MI). Propidium iodide (PI) was purchased from Sigma–Aldrich. Other reagents were obtained from Aladdin Reagent Co. Ltd. (China). All of the reagents were of analytical grade. All aqueous solutions were prepared with double-distilled water.

2.2. Preparation of CA-modified PDMS substrates

2.2.1. Preparation of PDMS substrates

PDMS elastomer (Sylgard® 184 silicone elastomer kit) solution is composed of a base (part A) and curing agent (part B). The base and curing agent were mixed in a 10:1 mass ratio, transferred to a glass Petri dish and cured for three days. After being sectioned into discs with a 14-mm diameter, the PDMS substrate was washed with 75% ethanol solution and dried with nitrogen.

2.2.2. PDMS substrate modification with CA

CA solution was prepared in double-distilled water at a concentration of 10 mg mL^{-1}. PDMS substrates were incubated in CA solution for 2 h at ambient conditions. Unattached CA was removed by rinsing the substrate with double-distilled water. The CA-modified PDMS substrates were dried with nitrogen.

2.3. Water contact angle (WCA) measurements

The WCAs of native PDMS and CA-modified PDMS surfaces were determined under ambient conditions using the sessile drop method and an optical contact angle meter (Dataphysics, Inc., OCA20). WCAs were averaged values from ten individual measurements that were collected from different regions on the PDMS surface. All of the measurements were within ±3° of the average. WCAs are presented as the average ± standard deviation.

2.4. X-Ray photoelectron spectroscopy (XPS) measurements

The modification of the PDMS substrate by CA was confirmed by an XPS apparatus (Thermofisher K-Alpha, USA) with a monochromatic Al Kα radiation source. The sample for XPS characterisation was deposited onto a Si slide. XPS analysis was performed on at least three samples before and after surface modification. The binding energy was swept from 0 to 1350 eV, and the photoelectron take-off angle was set at 45° in fixed analyser transmission mode. The energy resolution of the analyser was 0.9 eV.

2.5. Atomic force microscopy (AFM) measurements

The surface morphology of the PDMS substrates was analysed using atomic force microscopy (CSPM 4000, Being-Nano Inc., PR China). The images were scanned in tapping mode in air using commercial Si cantilevers (k = 40 N m^{-1}, Budget Sensors Inc., Bulgaria) with a resonance frequency of 300 kHz. Scan areas of 20 μm × 20 μm and 4.5 μm × 4.5 μm were collected at a 1 Hz scanning rate. Each sample was scanned at five random sites.

2.6. Molecular modelling and dynamics simulations

The coordinates of CA was obtained from the PRODRG server [22], and the conformation is consistent with recent research [23]. The initial structure of the PDMS substrate from our previously published work was used [24]. Briefly, a single PDMS chain consisting of 20 units was equilibrated in the gas phase for 10 ns. Twelve such chains were extracted from the last 2.4 ns of the trajectory and compressed into a slab of 55 Å × 55 Å × 11 Å to construct an amorphous supercell with a density of 0.92 g cm^{-3}. Unbound solid surfaces in the XY plane were modelled using periodic boundary conditions (PBCs). The adsorption of CA was performed using starting structures with their centre of mass (COM) placed >10 Å away from the surface. The assemblies were solvated along the Z-axis to avoid direct contact between CA and the substrate.

All molecular dynamics (MD) simulations were performed using the program NAMD 2.8 [25]. The topology and parameter files for CA were obtained and calculated using the ParamChem website, which is based on the CHARMM36 Generalised Force Field program. The parameters of PDMS were obtained from available literature, and the partial atomic charges were calculated using quantum chemistry [26,27]. The TIP3P water model was employed to model the aqueous solution [28]. PBCs were applied in the three directions of Cartesian space. Long-range electrostatic forces were taken into account using the particle mesh Ewald (PME) method, and a 14-Å cutoff was applied to truncate van der Waals interactions [29]. A temperature of 300 K and a pressure of 1 atm were used to ensure Langevin dynamics and the Langevin piston method [30]. Chemical bonds involving hydrogen atoms were constrained to their experimental lengths by SHAKE/RATTLE algorithms [31,32]. The equations of motion were integrated with a time step of 2 fs. Before production simulation, the molecular system for fixed CA was minimised using up to 5000 conjugate gradient (CG) steps prior to an additional geometry optimisation on the complete interaction using an equal amount of CG steps. A 2 ns MD simulation was subsequently generated with weak harmonic restraints enforced on CA, viz. 1.0 kcal/mol/Å^2. The restraints on CA were removed for the production run. All of the atoms of the PDMS substrate were fixed during the simulation. Visualisation and analysis of the MD trajectories were performed using the VMD program [33].

Because of the chemical inertness of PDMS, adsorption to PDMS usually occurs through physisorption. Therefore, only the initial association of CA with the PDMS substrates was explored. A crucial step in understanding this association is determining the free energy change of adsorption. It was recently demonstrated that the potential of mean force (PMF) is a computationally effective and accurate way to calculate the free energies of interacting substrates and molecules [34–36]. In the present study, PMF profiles that delineated the adsorption process of CA were estimated along the model adsorption pathway, which was defined as the projection onto the Z axis of the distance between the COM of a CA molecule

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