Ultrasmall Nanoparticle ROS Scavengers Based on Polyhedral Oligomeric Silsesquioxanes

Zhan Li, Haotian Li, Jianhua Zhang, Xianhu Liu, Zhipeng Gu, and Yiwen Li*

Abstract Although tremendous efforts have been devoted to the structural and functional tailoring of natural polyphenol-functionalized nanoparticles, preparing ultrasmall sized (< 6 nm) particles with precisely-defined structures has remained a grand challenge. In this work, we reported the preparation of ultra-small and precisely structured polyhedral oligomeric silsesquioxanes (POSS)-based polyphenol nanoparticles (T18, T10, and T12-GAPSOSS) by accurately functionalizing the POSS surface with plant polyphenol gallic acid units via thiol-Michael "click" reactions. Those polyphenol nanoparticles exhibited strong free radical scavenging capacity, good biocompatibility and ability to resist cell oxidative damage, which demonstrated great potentials in inhibiting oxidative stress induced pathologies.

Keywords Polyhedral oligomeric silsesquioxanes (POSS); Polyphenol; Ultrasmall nanoparticles; Free radical scavenging

INTRODUCTION

Oxidation stress is a crucial factor causing a series of pathological states due to irreversible oxidative damage of biological macromolecules and cell membranes.[1–3] When suffering illness or injury, the accumulation of reactive oxygen species (ROS) often exceeds the antioxidant capacity of the cells which need exogenous antioxidants to maintain the balance of redox in cells. Antioxidant nanoparticles with excellent free radical scavenging capacity have been regarded as the main therapeutic agents against oxidative stress damage over the past few decades. Nature can offer the sources and inspirations of antioxidants towards creating various nanomaterial ROS scavengers. For example, ubiquitous natural polyphenols could exhibit excellent antioxidation and free radical scavenging features, which could inspire the further design of biomimetic antioxidant materials based on a large variety of natural polyphenol building blocks.[4–11] One convenient way relied on the surface fabrication of established nanomaterials with natural polyphenol elements to construct nanoantioxidants with strong free radical scavenging capacity for inhibiting oxidative stress-induced diseases.[12–18] It was found that their antioxidant capacities highly depended on the specific surface area and surface density of polyphenol elements.[17,19,20] Although tremendous efforts have been devoted to the size tailoring of natural polyphenol-functionalized nanoparticles, preparing ultrasmall sized (< 5 nm) particles with ultrahigh polyphenol surface density has remained challenging. In addition, it was anticipated that achieving the structural precision might lead to antioxidant nanomaterials with finely tunable functions, but the conventional fabrication strategies usually lost the reliable control over the structures. Therefore, the construction of ultrasmall antioxidant nanoparticles with precisely-controlled structures remained a grand challenge towards more explorations of this class of biomaterials.

To address this issue, herein the polyhedral oligomeric silsesquioxanes (POSSs) with accurate structures were selected as the core blocks and gallic acid as the antioxidant functional element to construct ultrasmall sized nanoparticles with precisely-defined structures via a series of efficient chemical synthesis methods. There are several advantages to adopt this approach. Firstly, it is well known that POSS with an individual nanocage structure usually consists of an internal inorganic core and multiple peripheral organic functional groups, which is widely recognized as the smallest particle (~1 nm) available.[21–25] The use of POSSs as the building blocks to prepare the targeted materials allows the good control of the ultrasmall size of the resulting antioxidant nanoparticles. Secondly, POSS nanocages usually possess precisely defined chemical structures and multisite active groups that can be further transferred into a large variety of
functionalities via several efficient and precise chemical reactions like “click” chemistry. In this study, we employed thiol-functionalized gallic acid (SH-GA) and different commercially available acrylo POSS structures (T₈₋, T₁₀₋, T₁₂₋-ACPOSS) to synthesize a series of ultrasmall polyphenol nanoparticles (T₈₋, T₁₀₋, T₁₂₋-GAPOSS) (Scheme S1 in the electronic supplementary information, ESI) via thiol-Michael “click” reactions. All the resulting polyphenol nanoparticles possessed < 5 nm sizes, precisely-defined molecular structures, as well as strong antioxidant capacity and free radical scavenging ability (Scheme 1).

![Scheme 1](https://example.com/scheme1.png)

**Scheme 1** Material design and synthetic scheme toward POSS-based antioxidant nanoparticles.

**EXPERIMENTAL**

**General Considerations**

Gallic acid (J&K Scientific, 99%), MA0736-Acrylo POSS cage mixture (Hybrid Plastics, cage content > 90%), hexylamine (J&K Scientific, 98%), polyethylene glycol monomethyl ether 2k (Toyo Chemical Industry, TCI), tosyl chloride (Kelon Chemical, reagent grade), potassium bicarbonate (KHCO₃, J&K Scientific, 99.5%), 4-carboxyphenylboronic acid (Energy Chemical, 98%), N′-diisopropylcarbodiimide (DIPC, J&K Scientific, 99%), trifluoroacetic acid (TFA, J&K Scientific, 98%), 2-aminoethanol (Energy Chemical, 95%), N,N′-dissopropylcarbodiimide (DIPC, J&K Scientific, 99%), trifluoroacetic acid (TFA, J&K Scientific, 98%), phosphorus trichloride (Kelon Chemical, 99%), potassium bicarbonate (KHCO₃, J&K Scientific, 99.5%), 4-carboxyphenylboronic acid (Energy Chemical, 98%) (contains of anhydride), 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS, Tokyo Chemical Industry (TCI), ≥ 98.0%), 2,2-diphenyl-1-picrylhydrazyl (DPPH, Alfa Aesar, 95%), 1-hydroxybenzotriazole (HOBt, J&K Scientific, 98%), potassium persulfate (3.5 mmol/L) was added, and then the sample solution was added into it. In detail, deionized water (2.83 mL) was mixed with ABTS solution at different time.

**Characterization**

All ¹H, ¹³C, and ³¹P nuclear magnetic resonance (NMR) spectra were acquired in methylol-D₃ (Aldrich, 99.8% D) using a Bruker Av III HD 400 MHz spectrometer. Electrospray ionization-time of flight (ESI-TOF) was operated in positive or negative-ion mode on quadrupole orthogonal acceleration time-of-flight mass spectrometer (Q-TOF Premier, Waters Corporation, USA) using electron spray ionization as an ion source. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectroscopy (MS) was conducted on an Ultraflexxtreme MALDI-TOF mass spectrometer (Bruker Daltonics, Germany) equipped with a 1 kHz smart beam-II laser. The instrument was calibrated prior to each measurement with external PMMA at the molecular weight under consideration. The compound trans-3-[3-(4-tert-butyl-phenyl)-2-methyl-2-propenylidene]malononitrile (DCTB, Aldrich, > 98%) served as the matrix and was prepared in CHCl₃ at a concentration of 20 mg/mL. The cationizing agent sodium trifluoracetate was prepared in ethanol at a concentration of 10 mg/mL. All samples were dissolved in CHCl₃ at a concentration of 10 mg/mL. After sample preparation and solvent evaporation, the target plate was inserted into the MALDI-TOF mass spectrometer. The attenuation of the laser was adjusted to minimize undesired polymer fragmentation and to maximize the sensitivity. Infrared spectra were obtained on a NICOLET iS50 FTIR spectrometer (Thermo Scientific) by grinding samples with specially purified potassium bromide (KBr) in the quartz mortar to remove scattering effects from large crystals, then pressed in a mechanical press to form a translucent round thin slice. The spectroscopic data were processed using OMNIC software. Dynamic light scattering (DLS) data were measured on a Malvern Nano-ZS ZEN690 at 25 °C. Samples were dispersed in ultra-pure dimethylsulfoxide (DMSO) by ultrasound.

**Free Radical Scavenging**

DPPH free radical scavenging

We use standard 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay to evaluate the radical scavenging activities of different samples. A fresh DPPH/ethanol (1 mmol/L) solution was used for the measurements. The samples (T₈₋-GAPOSS, T₁₀₋-GAPOSS, and T₁₂₋-GAPOSS) were configured into ethanol solution (0.5, 1.0, 1.5, and 2.0 μg/mL). Ethanol (2.6 mL) was mixed with DPPH solution (300 μL), and then 100 μL of sample solution was added into it. The scavenging activity was evaluated by measuring the absorbance at 517 nm after mixing the sample with DPPH solution at different time.

**ABTS⁺ free radical scavenging**

ABTS⁺ radical preparation: 82.3 mg of ABTS (10 mmol/L) was dissolved in 15 mL of aqueous solution and 14.19 mg of potassium persulfate (3.5 mmol/L) was added, and then the solution was stirred in the dark for 16 h. In detail, deionized water (2.83 mL) was mixed with ABTS⁺ solution (70 μL), and then 100 μL of sample solution (T₈₋-GAPOSS/PBA-PEG, T₁₀₋-GAPOSS/PBA-PEG, and T₁₂₋-GAPOSS/PBA-PEG) was added to it. The scavenging activity was evaluated by measuring the absorbance at 734 nm after mixing the sample with ABTS⁺ solution at different time.

**Cell Culture**

The third generation of NIH 3T3 cells were used as the cell line for test and cultured in Dulbecco’s Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum, maintaining at 37 °C in 5% CO₂ and a humidified atmosphere.

**Cytocompatibility Testing**

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed to evaluate the cell viability of each sample. Briefly, NIH 3T3 cells were incubated in 96-well
plates at a density of 1000 cells per well for 24 h. The cells were treated with different samples at different concentrations for another 24, 72 and 120 h. The corresponding cell viability was evaluated by the MTT assay. For the live/dead viability staining, the NIH 3T3 cells were cultured with each sample and incubated for 1, 2 or 3 days before the staining with calcein-AM as well as ethidium homodimer (Thermo Fisher Scientific Inc. USA). After staining the cells were observed on the Zeiss Axio Observer Z1 (Germany) and the fluorescence images were recorded.

**Intracellular Oxidative Stress of NIH 3T3 Cells**

The level of ROS was measured byDCFH-DA staining. Briefly, the NIH 3T3 cells with a density of 5 × 10⁴ cells per well were incubated in 24-well plates for 12 h, and pre-treated with T₈-, T₁₀-, T₁₂-GAPPOSS/PBA-PEG, T₁₀-GAPPOSS/PBA-PEG, and T₁₂-GAPPOSS/PBA-PEG (50 μg/ml) for another 24 h, and then were treated with 100 μmol/L H₂O₂ at 37 °C for 24 h. Cells were stained with DCFH-DA (10 μmol/l) for 10 min at 37 °C in the dark. Samples were analyzed by flow cytometer and fluorescence microscope (Carl Zeiss, Germany). In addition, the oxidative stress indicators (GSH/GSSG and SOD) were measured by using assay kits (Beyotime, China) according to the manufacturer’s instructions.

**RESULTS AND DISCUSSION**

The detailed material design and chemical reactions were proposed to prepare the ultrasmall antioxidant nanoparticles (T₈-, T₁₀-, T₁₂-GAPOSS, Fig. 1A) according to Scheme S1 (in ESI). Note that the polyphenol structure might also undergo Michael addition or Schiff base reactions with functional amino or thiol groups under basic conditions, so we used the thiol-modified acetonide protected gallic acid (AP-GA-SH) (see the detailed characterizations and Figs. S1−S3 in ESI) and three kinds of acetonide protected gallic acid (AP-GA-SH) (see the detailed characterizations and Figs. S4 and S5 in ESI) to perform the conjugation reaction. The successful thiol-Michael “click” conjugation of AP-GA-SH with GAPPOSS was evident from the disappearance of methyl group signal at δ 6.38−5.81 ppm (−CH=CH₂) and the appearance of new signals of δ 6.95 ppm (−CH=−), δ 6.78 ppm (−CH=−) and δ 1.66 ppm (−CH₃) in the ¹H-NMR spectra (Figs. S6–S8 in ESI). Moreover, the peaks observed at m/z 3497.1, 4365.4 and 5234.7 (Na⁺ adduct) in the MALDI-TOF mass spectra agreed well with the calculated monoisotopic molecular mass of T₈-, APGAPOSS ([M-Na]⁺: 3496.8), T₁₀-APGAPOSS ([M-Na]⁺: 4365.0) and T₁₂-APGAPOSS ([M-Na]⁺: 5234.2) in DMSO were measured as 4.0, 4.4, and 5.8 nm, respectively (Figs. 2a–2c). In addition, the CS section was performed via the DMol3 module in Materials Studio 7.0 software package, which also showed the theoretical sizes of those samples (T₈-, T₁₀-, and T₁₂-GAPPOSS) in DMSO are 4.3, 4.3, and 4.4 nm, respectively (Fig. 2d). Both DLS and CS results clearly demonstrated the ultrasmall sizes (< 5 nm) of those antioxidant nanoparticles (Fig. 2e). Moreover, according to the simulation results, it can be further estimated that the surface of those antioxidant nanoparticles (T₈-, T₁₀-, and T₁₂-GAPPOSS) possesses 8.7, 8.3, and 7.8 gallic acid units/nm², again confirming their high surface density of polyphenol elements.

It is well known that the phenolic hydroxyl groups of natural or synthetic polyphenol materials are easily oxidized to quinones structure, which can rapidly consume the oxygen and ROS in the environment. Therefore, we believed that those GAPPOSSs containing plant polyphenol units with high surface density could demonstrate strong free radical scavenging and antioxidant capacity. The popularly used 2,2-diphenyl-1-picrylhydrazyl (DPPH) testing was performed to measure the free radical scavenging activities of T₈-, T₁₀-, and T₁₂-GAPPOSS nanoparticles in the organic phase (Scheme S2 in ESI). In detail, their free radical scavenging activities were measured by detecting the decrease in absorbance at 517 nm from 0.1 mmol/L DPPH ethanol solution (3 mL) after incubation with 50, 100, 150 and 200 μg of samples at different time points, respectively. For example, Fig. 3(a) shows the UV-Vis absorption spectra of DPPH solution (0.1 mmol/L, 3 mL) after the addition of T₈-GAPOSS nanoparticles, and it was found that the absorption peak intensity at 517 nm was decreasing

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gradually. The free radical scavenging capabilities of the GAPOSSs were increasing with the increase of sample concentration and incubation time (Fig. S14 in ESI). As shown in Fig. 3(b), all the samples exhibited excellent free radical scavenging performances and their radical scavenging rates were all quite fast. For instance, when the incubation time was close to 30 min, the free radical scavenging efficiency could reach more than 90% for all antioxidant samples, which was consistent with the rapid color change of DPPH solution. Interestingly, note that those polyphenol nanoparticles all demonstrated better radical scavenging activities than polydopamine (PDA) nanoparticle (~200 nm), a well-known and widely used nanoantioxidant, in the DPPH testing array. Similar results were also obtained by the 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)diammonium salt (ABTS) testing performed in the aqueous solution using ABTS radical cations (ABTS⁺) as the radical donor (Scheme S2 in ESI). In order to improve the solubility of polyphenol nanoparticles, the POSS-GA/PBA-PEG (MPOSS-GA/MPEG = 1/2) complex samples were directly prepared by means of the acid-sensitive dynamic chemical bond formed between the catechol structure on the surface of polyphenol nanoparticles and methyl terminated polyethylene glycol phenylboric acid (PBA-PEG) (Fig. S15 in ESI), which can be dissociated under the inflammatory acidic microenvironment induced by oxidative stress and completely exposing the polyphenol structure of nano-
Fig. 2  DLS results of (a) T₈-GAPOSS, (b) T₁₀-GAPOSS and (c) T₁₂-GAPOSS; (d) Calculation of particle size of T₈-GAPOSS, T₁₀-GAPOSS and T₁₂-GAPOSS by CS; (e) Particle size data of antioxidant nanoparticles by DLS and CS.

Fig. 3  (a) UV-Vis absorption spectra of DPPH solution after the addition of 100 μg of T₈-GAPOSS nanoparticles; (b) DPPH radical scavenging activities of T₈-GAPOSS, T₁₀-GAPOSS, T₁₂-GAPOSS and PDA incubation with 100 μg at different incubation time. The inserted image is the color contrast before and after adding 100 μg of T₈-GAPOSS and incubating for 30 min; (c) UV-Vis absorption spectra of ABTS solution after the addition of 100 μg of T₈-GAPOSS nanoparticles; (d) ABTS scavenging activities of T₈-GAPOSS/PBA-PEG, T₁₀-GAPOSS/PBA-PEG and T₁₂-GAPOSS/PBA-PEG (100 μg/200 μg). The inserted image is the color contrast before and after adding 100 μg of T₈-GAPOSS/PBA-PEG and incubating for 30 min.

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particles. According to Fig. 3(c), the absorption peak at 735 nm can be obtained as the characteristic absorption peak for detecting ABTS** free radical scavenging. Their free radical scavenging activities could be measured by monitoring the change trend of the absorbance of ABTS** and GAPOSS/PBA-PEG aqueous solutions within 30 min. As shown in Fig. 3(d), the free radical scavenging efficiency can reach more than 55% when incubated for 30 s. And when the incubation time reached 30 min, the free radical scavenging rate was more than 70% for all antioxidant samples, which matched well with the color change of the APTS solutions. However, the ABTS** free radical scavenging capacity of PDA nanoparticle was only 35% under the same test conditions. The promising radical scavenging properties of those POSS-based polyphenol nanoparticles are due to the high density of gallic acid units on the particle surface and the ultrasmall size of the particle, suggesting their potentials as highly efficient ROS scavengers for biomedical applications.

We further evaluated the antioxidant performances of those POSS-based polyphenol nanoparticles in protecting cells from oxidative stress. Before that, the good biocompatibility of those polyphenol nanoparticles was verified by MTT colorimetric (samples concentration 1–500 μg/mL particle, incubated 24, 72 and 120 h, respectively) and Calcein-AM/PI staining method (Figs. S16a and S16b in ESI). NIH 3T3 cells were first exposed to 100 μmol/L H₂O₂ for oxidative stimulation, and then treated with T⁸⁻, T₁₀⁻, and T₁₂⁻GAPOSS/PBA-PEG (GAPOSS and PBA-PEG sample concentrations were 16.7 and 33.3 μg/mL) for 24 h. As expected (Figs. 4a and 4b), it could be seen that after 24 h of incubation, the ROS level of NIH 3T3 cells in the control group increased significantly, while the level of ROS could be significantly inhibited by treating with these ultrasmall and precisely regulated nanoparticles. Furthermore, the ratio of glutathione and glutathione disulfide (GSH/GSSG) and the contents of superoxide dismutase (SOD) in the cytoplasm of NIH 3T3 cells were quantitatively analysed to confirm the antioxidant behaviour of these nanoparticles. As shown in Figs. 4(c) and 4(d), the ratio of GSH/GSSG and concentration of SOD in the cells treated with those polyphenol nanoparticles were remarkably higher than the control group, indicating that polyphenol nanoparticles showed a better effect in preventing ROS oxidative damage of the cells. All the above results clearly showed that those POSS-based polyphenol nanoparticles can effectively alleviate the oxidative stress injury of the cells, which is due to the scavenging effects of multiple ROS in the intracellular environments for preventing cell oxidative damage. Above all, those antioxidant polyphenol nanoparticles exhibit good biocompatibility and excellent ROS scavenging capacity on the cellular level, and the fine-turning of intracellular antioxidant index (GSH/GSSG and SOD) can be realized by accurately regulating the number of

Fig. 4 (a) Fluorescent microscope images of ROS levels in H₂O₂-treated NIH 3T3 cells incubated with different POSS-based polyphenol nanoparticles (50 μg/mL) for 1 day; (b) Quantitative detection of active oxygen. DCFH-DA was used as the fluorescence. (c) GSH/GSSG and (d) SOD contents of H₂O₂-treated cells with 50 μg/mL sample treatment after 1 day. PC: positive control. **p < 0.01, ***p < 0.001, ****p < 0.0001.
gallic acid units on the particle surface. Compared with the traditional polyphenol antioxidant nanoparticles with uncontrolled structure and function, the ultra-small nanoparticles with precise structural regulation are of great significance for the future study of the mechanism of polyphenol antioxidant materials inhibiting oxidative stress in vivo.

CONCLUSIONS

In summary, we reported the preparation of ultra-small and precisely structured POSS-based polyphenol nanoparticles ($T_{\text{g}}$, $T_{\text{g}}$, and $T_{\text{g}}$-GAPOSS) by accurately functionalizing the POSS surface with plant polyphenol gallic acid units. Those polyphenol nanoparticles exhibited strong free radical scavenging capacity, good biocompatibility and ability to resist cell oxidative damage, which demonstrated great potentials in inhibiting oxidative stress induced pathologies.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of charge in the online version of this article at https://doi.org/10.1007/s10118-020-2486-7.

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REFERENCES

1. Cairns, R. A.; Harris, I. S.; Mak, T. W. Regulation of cancer cell metabolism. Nat. Rev. Cancer. 2011, 11, 85.
2. Jiao, X.; Li, Y.; Niu, J.; Xie, X.; Wang, X.; Tang, B. Small-molecule fluorescent probes for imaging and detection of reactive oxygen, nitrogen, and sulfur species in biological systems. Anal. Chem. 2017, 90, 533–555.
3. Zhang, J.; Fu, Y.; Yang, P.; Liu, X.; Li, Y.; Gu, Z. ROS scavenging biopolymers for anti-inflammatory diseases: classification and formulation. Adv. Mater. Interfaces 2020, 4, 2000632.
4. Wang, C.; Sang, H.; Wang, Y.; Zhu, F.; Hu, X.; Wang, X.; Wang, X.; Li, Y.; Cheng, Y. Foe to friend: supramolecular nanomedicines consisting of natural polyphenols and bortezomib. Nano Lett. 2018, 18, 7045–7051.
5. Rahim, M. A.; Kristufek, S. L.; Pan, S.; Richardson, J. J.; Caruso, F. Phenolic building blocks for the assembly of functional materials. Angew. Chem. Int. Ed. 2019, 58, 1904–1927.
6. Dai, Q.; Geng, H.; Yu, Q.; Hao, J.; Cui, J. Polyphenol-based particles for theranostics. Theranostics 2019, 9, 3170.
7. Shin, M.; Park, E.; Lee, H. Plant-inspired pyrogallol-containing functional materials. Adv. Funct. Mater. 2019, 29, 1903022.
8. Li, M.; Wang, H.; Hu, J.; Hu, J.; Zhang, S.; Yang, Z.; Li, Y.; Cheng, Y. Smart hydrogels with antibacterial properties built from all natural building blocks. Chem. Mater. 2019, 31, 7678–7685.
9. Yang, P.; Zhang, S.; Chen, X.; Liu, X.; Wang, Z.; Li, Y. Recent developments in polydopamine fluorescent nanomaterials. Mater. Horiz. 2020, 7, 746–761.
10. Wang, X.; Yang, L.; Yang, P.; Guo, W.; Zhang, Q.; Liu, X.; Li, Y. Metal ions-promoted fabrication of melanin-like poly(L-DOPA) nanoparticles for photothermal actuation. Sci. China Chem. 2020, 63, 1295–1305.
11. Shi, X.; Yang, P.; Peng, X.; Huang, C.; Qian, Q.; Wang, B.; He, J.; Liu, X.; Li, Y.; Kuang, T. Bi-phase fire-resistant polyethyleneimine/graphene oxide/melanin coatings using layer by layer assembly technique: smoke suppression and thermal stability of flexible polyurethane foams. Polymer 2019, 170, 65–75.
12. Valigimili, L.; Baschieri, A.; Amorati, R. Antioxidant activity of nanomaterials. J. Mater. Chem. B 2018, 6, 2036–2051.
13. Hsieh, D. S.; Wang, H.; Tan, S. W.; Huang, Y. H.; Tsai, C. Y.; M.; Wu, C. J. The treatment of bladder cancer in a mouse model by epigallocatechin-3-gallate-gold nanoparticles. Biomaterials 2011, 32, 7633–7640.
14. Lin, Y. H.; Chen, Z. R.; Lai, C. H.; Hsieh, C. H.; Feng, C. L. Active targeted nanoparticles for oral administration of gastric cancer therapy. Biomacromolecules 2015, 16, 3021–3032.
15. Shutava, T. G.; Balkundi, S. S.; Vangala, P.; Steffan, J. J.; Bigelow, R. L.; Cardelli, J. A.; O’Neal, D. P.; Lvov, Y. M. Layer-by-layer coated gelatin nanoparticles as a vehicle for delivery of natural polyphenols. ACS Nano 2009, 3, 1877–1885.
16. Debndath, K.; Shekhar, S.; Kumar, V.; Jana, N. R.; Jana, N. R. Efficient inhibition of protein aggregation, disintegration of aggregates, and lowering of cytotoxicity by green tea polyphenol-based self-assembled polymer nanoparticles. ACS Appl. Mater. Interfaces 2016, 8, 20309–20318.
17. Xiang, S.; Yang, P.; Guo, H.; Zhang, S.; Zhang, X.; Zhu, F.; Li, Y. Green tea makes polyphenol nanoparticles with radical-scavenging activities. Macromol. Rapid Commun. 2017, 38, 1700446.
18. Hu, K.; Miao, L.; Goodwin, T. J.; Li, J.; Liu, Q.; Huang, L. Quercetin remodels the tumor microenvironment to improve the permeation, retention, and antitumor effects of nanoparticles. ACS Nano 2017, 11, 4916–4925.
19. Ju, K.-Y.; Lee, Y.; Lee, S.; Park, S. B.; Lee, J. K. Biospired polymerization of dopamine to generate melanin-like nanoparticles having an excellent free-radical-scavenging property. Biomacromolecules 2011, 12, 625–632.
20. Wang, X.; Chen, Z.; Yang, P.; Hu, J.; Wang, Z.; Li, Y. Size control synthesis of melanin-like polydopamine nanoparticles by tuning radicals. Polym. Chem. 2019, 10, 4194–4200.
21. Cordes, D. B.; Lickiss, P. D.; Rataboul, F.; Fataoub, F. Recent developments in the chemistry of cubic polyhedral oligosilsesquioxanes. Chem. Rev. 2010, 110, 2081–2173.
22. Li, Z.; Kong, J.; Wang, F.; He, C. Polyhedral oligomeric silsesquioxanes (POSSs): an important building block for organic optoelectronic materials. J. Mater. Chem. C 2017, 5, 5283–5298.
23. Hou, H.; Li, J.; Li, X.; Forth, J.; Yin, J.; Jiang, X.; Helms, B. A.; Russell, T. P. Interfacial activity of amine-functionalized polyhedral oligomeric silsesquioxanes (POSS): a simple strategy to structure liquids. Angew. Chem. Int. Ed. 2019, 131, 10248–10253.
24. Li, Z.; Hu, J.; Yang, L.; Zhang, X.; Liu, X.; Wang, Z.; Li, Y. Integrated POSS-dendrimer nanohybrid materials: current status and future perspective. Nanoscale 2020, 12, 11395–11415.
25. Su, Z.; Zhang, R.; Yan, X.; Guo, Q.; Huang, J.; Shan, W.; Liu, Y.; Liu, T.; Huang, M.; Cheng, S. Z. The role of architectural engineering in macromolecular self-assemblies via non-covalent interactions: a molecular LEGO approach. Prog. Polym. Sci. 2020, 103, 101230.
26. Li, Z.; Fu, Y.; Li, Z.; Nan, N.; Zhu, Y.; Li, Y. Froth flotation giant surfactants. Polymer 2019, 162, 58–62.
27. Zhou, K.; Bisoyi, H. K.; Jin, Q. J.; Yuan, C. L.; Liu, Z.; Shen, D.; Lu, Y. Q.; Zheng, Z. G.; Zhang, W.; Li, Q. Light-driven reversible
transformation between self-organized simple cubic lattice and helical superstructure enabled by a molecular switch functionalized nanocage. Adv. Mater. 2018, 30, 1800237.

28 Kuo, S. W.; Chang, F. C. POSS related polymer nanocomposites. Prog. Polym. Sci. 2011, 36, 1649–1696.

29 Jeon, J. H.; Tanaka, K.; Chujo, Y. Synthesis of sulfonic acid-containing POSS and its filler effects for enhancing thermal stabilities and lowering melting temperatures of ionic liquids. J. Mater. Chem. A 2014, 2, 624–630.

30 Li, Y.; Dong, X. H.; Zou, Y.; Wang, Z.; Yue, K.; Huang, M.; Liu, H.; Feng, X.; Lin, Z.; Zhang, W.; Cheng, S. Z. Polyhedral oligomeric silsesquioxane meets “click” chemistry: rational design and facile preparation of functional hybrid materials. Polymer 2017, 125, 303–329.

31 Zhang, W.; Müller, A. H. Architecture, self-assembly and properties of well-defined hybrid polymers based on polyhedral oligomeric silsequioxane (POSS). Prog. Polym. Sci. 2013, 38, 1121–1162.

32 Lu, N.; Lu, Y.; Liu, S.; Jin, C.; Fang, S.; Zhou, X.; Li, Z. Tailor-engineered POSS-based hybrid gels for bone regeneration. Biomacromolecules 2019, 20, 3485–3493.

33 Su, Z.; Hsu, C. H.; Gong, Z.; Feng, X.; Huang, J.; Zhang, R.; Wang, Y.; Mao, J.; Wesdemiotis, C.; Li, T.; Cheng, S. Z. Identification of a Frank-Kasper Z phase from shape amphiphile self-assembly. Nat. Chem. 2019, 11, 899–905.

34 Zou, Y.; Zhang, L.; Yang, L.; Zhu, F.; Ding, M.; Lin, F.; Wang, Z.; Li, Y. “Click” chemistry in polymeric scaffolds: bioactive materials for tissue engineering. J. Control. Release 2018, 273, 160–179.

35 Shavandi, A.; Bekhit, A. E. D. A.; Saeedi, P.; Izadifar, Z.; Bekhit, A. A.; Khademhosseini, A. Polyphenol uses in biomaterials engineering. Biomaterials 2018, 167, 91–106.

36 Yang, P.; Gu, Z.; Zhu, F.; Li, Y. Structural and functional tailoring of melanin-like polydopamine radical scavengers. CCS Chem. 2020, 2, 128–138.

37 Li, Z.; Wang, T.; Zhu, F.; Wang, Z.; Li, Y. Bioinspired fluorescent dihydroxyindoles oligomers. Chin. Chem. Lett. 2020, 31, 783–786.

38 Cheng, X.; Li, M.; Wang, H.; Cheng, Y. All-small-molecule dynamic covalent gels with antibacterial activity by boronate-tannic acid gelation. Chin. Chem. Lett. 2020, 31, 869–874.

39 Li, Z.; Zhang, J.; Fu, Y.; Yang, L.; Zhu, F.; Liu, X.; Gu, Z.; Li, Y. Antioxidant shape amphiphiles for accelerated wound healing. J. Mater. Chem. B 2020, 8, 7018–7023.

40 Shan, M.; Gong, C.; Li, B.; Wu, G. A pH, glucose, and dopamine triple-responsive, self-healable adhesive hydrogel formed by phenylborate-catechol complexation. Polym. Chem. 2017, 8, 2997–3005.