

Article

Self-Assembled Berberine-Sinapic Acid Nanomedicine for Synergistic Chemotherapy

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Abstract

Breast cancer ranks among the most prevalent malignant tumors globally, underscoring the urgent need for efficient and low-toxicity treatment strategies. In this study, a novel nanomedicine (BBR-SA) was constructed based on the self-assembled of berberine (BBR) and sinapic acid (SA) for synergistic chemotherapy. Firstly, utilizing π - π stacking, hydrogen bonding, and electrostatic forces between BBR and SA, the BBR-SA achieved a well-defined nanostructure with high drug-loading capacity and favorable water dispersibility. Furthermore, BBR-SA nanomedicine effectively inhibited the proliferation of mouse mammary carcinoma cells (4T1), showing a significantly stronger inhibitory effect than either BBR or SA alone. Moreover, the remarkable anti-tumor effect was obtained after treatment with BBR-SA nanomedicine in vivo, further demonstrating a synergistic therapeutic effect. More importantly, no significant systemic toxicity was observed after 28 days of intravenous administration with BBR-SA nanomedicine. In summary, the BBR-SA nanomedicine represents a safe and effective therapeutic strategy for breast cancer, offering new perspectives on the application of the traditional chinese medicine in anti-tumor therapy.

Keywords: traditional chinese medicine; self-assembly; berberine; sinapic acid; synergistic chemotherapy

1. Introduction

Currently, chemotherapy remains a mainstay in the clinical treatment of breast cancer [1–3]. However, conventional chemotherapy drugs are associated with significant serious side effects and may induce multi-drug resistance (MDR), thereby substantially limiting therapeutic efficacy [4–6]. Recently, compounds derived from traditional Chinese medicine (TCM) have garnered considerable attention in oncology research. This interest stems from the observed potential of certain TCM compounds to reduce toxicity, enhance efficacy, and reverse chemotherapy resistance in some studies [7,8]. However, most traditional chinese medicine exhibit poor water solubility, resulting in low bioavailability and thus limiting their clinical application [9,10]. Hence, designing novel medicine delivery systems that significantly improve the water-solubility of traditional chinese medicine while achieving favorable chemotherapeutic outcomes is of great significance for safe and efficient breast cancer treatment.

Berberine (BBR) is a benzyloquinoline alkaloid commonly isolated from a variety of medicinal plants [11,12]. It exhibits multiple pharmacological activities such as anti-inflammatory [13], anti-bacterial [14], anti-viral [15] and so on. Furthermore, BBR can eliminate tumor cells via multiple mechanisms, including inhibiting tumor cell proliferation, inducing apoptosis, and suppressing tumor angiogenesis [16–18]. More importantly, the



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positively charged quaternary ammonium ion in BBR can attract negatively charged groups (such as carboxyl and hydroxyl groups) through electrostatic interactions, thereby enabling BBR to self-assemble with other drugs to form nanostructure [19–21]. Additionally, the presence of benzene rings in BBR facilitates π - π stacking interactions, further promoting the self-assembly process [22,23]. This not only significantly enhances the water-solubility of traditional chinese medicine but also enables carrier-free drug delivery with a high loading capacity.

Sinapic acid (SA) is a natural phenolic acid widely present in cruciferous plants [24–26]. Research has found that SA can suppress tumor metastasis by regulating multiple signaling pathways, indicating its potential value in cancer treatment [27–29]. Another important aspect is that SA contains negatively charged carboxyl and phenolic hydroxyl groups [30], allowing for electrostatic attraction with the positively charged quaternary ammonium ion in BBR. Additionally, both SA and BBR possess benzene rings that favor π - π stacking interactions. Based on this, we speculate that BBR and SA can undergo self-assembly to create nanomedicine. To our best knowledge, there is no report on the self-assembly of BBR and SA into nanostructures.

Given the favorable anti-tumor activities of BBR and SA and their structural advantages, this study constructed a novel nanomedicine (BBR-SA) via self-assembly of BBR and SA for synergistic chemotherapy (Figure 1). BBR-SA nanomedicine demonstrated a high loading efficiency, with a loading rate of 21.05% for SA and 31.12% for BBR. Besides, it exhibited good dispersibility in various media including ultrapure water, PBS, and fetal bovine serum (FBS). Furthermore, BBR-SA nanomedicine significantly outperformed both free BBR and SA in terms of tumor cell cytotoxicity and in vivo anti-tumor effects, highlighting the clear synergistic advantage of the combined formulation. Additionally, BBR-SA nanomedicine showed no significant bio-toxicity after injection for 28 days. In summary, by self-assembling BBR and SA into a novel nanomedicine, this study not only overcomes the inherent limitations of traditional chinese medicine but also achieves synergistic chemotherapeutic effects, providing a new feasible therapeutic strategy for breast cancer treatment.

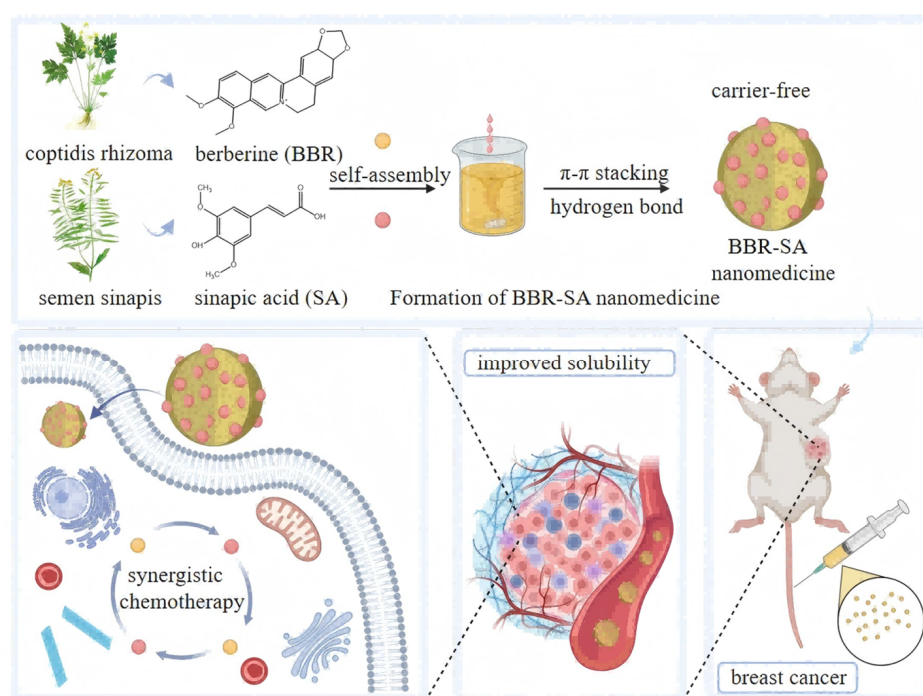


Figure 1. Self-assembled BBR-SA nanomedicine for synergistic chemotherapy.

2. Results

2.1. Synthesis and Characterization of BBR-SA Nanomedicine

The BBR-SA nanomedicine was prepared by first mixing 27 mg BBR and 18 mg SA, followed by stirring the mixture in PBS at 60 °C for 15 min. The final product was then obtained via dialysis against PBS for 12 h. Firstly, we observed its morphology by the transmission electron microscopy (TEM). As shown in the Figure 2a, BBR-SA nanomedicine exhibited a spherical shape with uniform size of approximately 50–60 nm. Subsequently, the dynamic light scattering (DLS) was employed to assess the dispersion stability of BBR-SA in various media. After dispersion in ultrapure water, PBS, and FBS for 24 h, the size distribution trends of BBR-SA nanomedicine remained almost consistent, with an average hydrodynamic diameter of 108 nm (Figure 2b). These results indicated the good dispersibility of BBR-SA nanomedicine. Furthermore, the zeta potential of BBR was measured as +20.21 mV, which was largely due to its positively charged quaternary ammonium group. In contrast, SA exhibited a negative zeta potential of −17.56 mV, primarily resulting from the carboxyl and phenolic hydroxyl groups in its structure. Notably, the zeta potential of the BBR-SA nanomedicine was recorded at +6.46 mV, a value intermediate between those of BBR and SA, indicating the successful self-assembly (Figure 2c). Then, we examined the ultraviolet-visible (UV-Vis) absorption spectra of BBR, SA, and BBR-SA. Figure 2d showed that the characteristic absorption peaks of BBR appeared at 262 and 349 nm, whereas SA exhibited a characteristic absorption peak at 322 nm. It's worth noting that an absorption peak at 265 nm was observed in the BBR-SA nanomedicine, along with a combined peak at 335 nm integrating absorption at 322 and 349 nm, confirming its successful synthesis. Additionally, the drug loading capacities of SA and BBR in the BBR-SA nanomedicine was determined to be 21.05% and 31.12%, respectively (Figures S1 and S2). Furthermore, we analyzed the Fourier transform infrared (FT-IR) spectra of BBR, SA, and BBR-SA. As shown in Figure 2e, BBR displayed characteristic peaks at 1107 and 1037 cm^{-1} , attributed to C-N stretching vibrations and alicyclic ether groups, respectively. These characteristic peaks remained clearly discernible in BBR-SA nanomedicine. Additionally, the peak at 1660 cm^{-1} in the SA corresponds to the C=O stretching of the carboxyl group (Figure 2f). However, this peak exhibited a noticeable blueshift in the spectrum of BBR-SA nanomedicine, indicating a reduction in the electron cloud density of the carbonyl group. This result suggested that the carboxyl group served as a binding site for BBR and SA, with interactions involving hydrogen bonding and π - π stacking [31]. Moreover, the stretching vibration of the C=O was significantly reduced, indicating electrostatic interactions between the quaternary ammonium cation in BBR and the carboxyl group in SA. Furthermore, the absorption peak of SA at 3376.7 cm^{-1} confirmed the presence of the phenolic hydroxyl (O-H) group. And this peak broadened in the BBR-SA nanomedicine, further supporting the formation of hydrogen bonds between SA and BBR. These above results demonstrate that BBR and SA self-assemble into BBR-SA nanomedicine through hydrogen bonding, electrostatic interactions, and π - π stacking interactions.

2.2. Cytotoxicity and Anti-Tumor Efficacy of BBR-SA Nanomedicine

Given the excellent biocompatibility of BBR-SA nanomedicine, we further conducted its anti-tumor performance in vitro. Firstly, mouse embryonic fibroblasts (3T3) cells were selected as a typical model to investigate the cytotoxicity of BBR-SA nanomedicine. As shown in the Figure S3, even after 24 h of co-incubation with BBR-SA nanomedicine at a concentration of 200 $\mu\text{g}/\text{mL}$, the viability of 3T3 cells remained as high as 66.05%, confirming the hypotoxicity of BBR-SA nanomedicine towards normal cells. Subsequently, Mouse breast cancer (4T1) cells were chosen as a representative model to evaluate the anti-tumor efficacy of BBR-SA nanomedicine in vitro. Fluorescein isothiocyanate (FITC)-labeled BBR-

SA nanomedicine was prepared by incubating BBR-SA nanomedicine with FITC under continuous stirring overnight. Then, 4T1 cellular uptake was assessed using inverted fluorescence microscopy after treated with the FITC-labeled BBR-SA nanomedicine for 1, 2, and 4 h, respectively. As shown in Figure 3a, the green fluorescence intensity of FITC-labeled BBR-SA nanomedicine exhibited a marked increase within cells over 4 h, demonstrating its high cellular uptake efficiency. Thereafter, the cell counting kit-8 (CCK-8) assay was employed to evaluate the anti-tumor efficacy of the BBR-SA nanomedicine. As shown in Figure 3b,c, both free BBR and SA displayed modest cytotoxic efficacy against 4T1 cells. Notably, BBR-SA nanomedicine induced significantly enhanced cell lethality compared to the free drug at equivalent concentrations. Strikingly, nearly complete eradication of 4T1 cells was observed after 24 h treatment with 200 $\mu\text{g}/\text{mL}$ BBR-SA nanomedicine (Figure 3d,e). All these findings indicated that BBR-SA nanomedicine possessed remarkable combined chemotherapeutic efficacy.

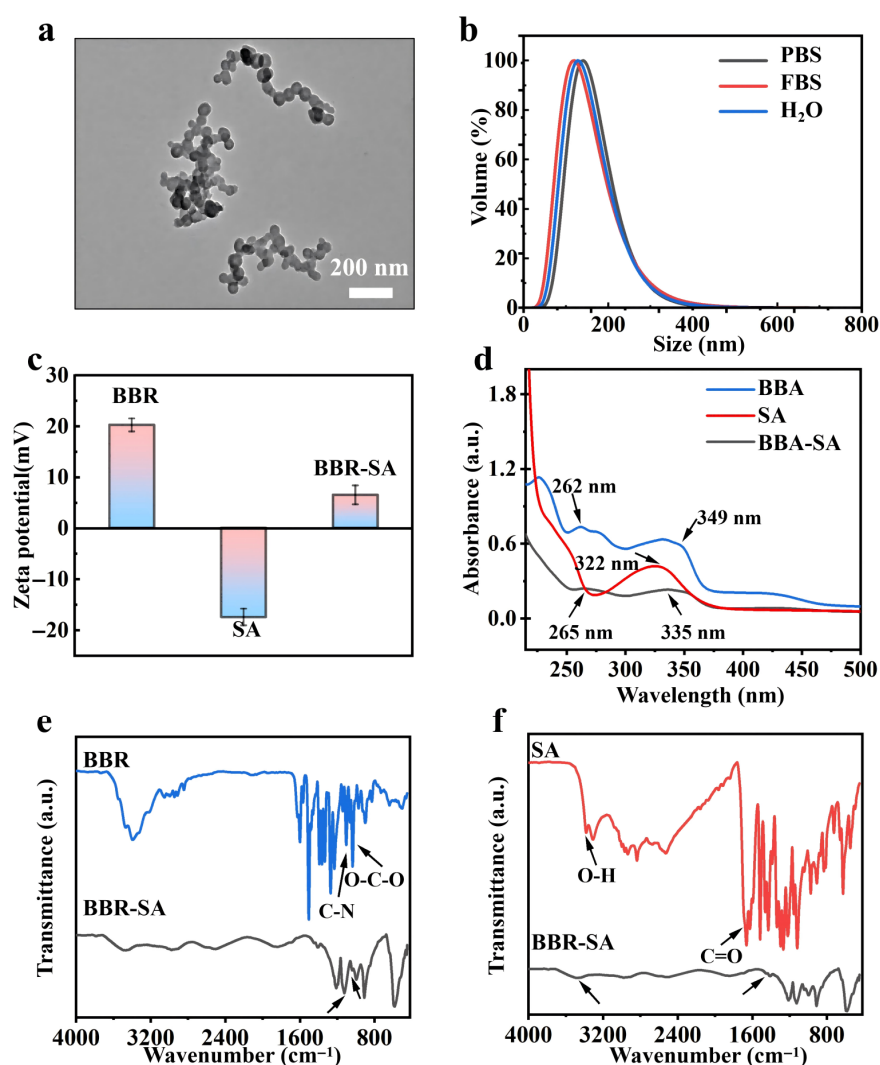


Figure 2. (a) TEM morphology of BBR-SA nanomedicine. (b) Hydrodynamic diameter of BBR-SA nanomedicine in ultrapure water, PBS, and FBS. (c) Zeta potential of BBR, SA, and BBR-SA nanomedicine. (d) UV-Vis spectra of BBR, SA, and BBR-SA nanomedicine. FT-IR spectra of (e) BBR and BBR-SA nanomedicine, (f) SA and BBR-SA nanomedicine.

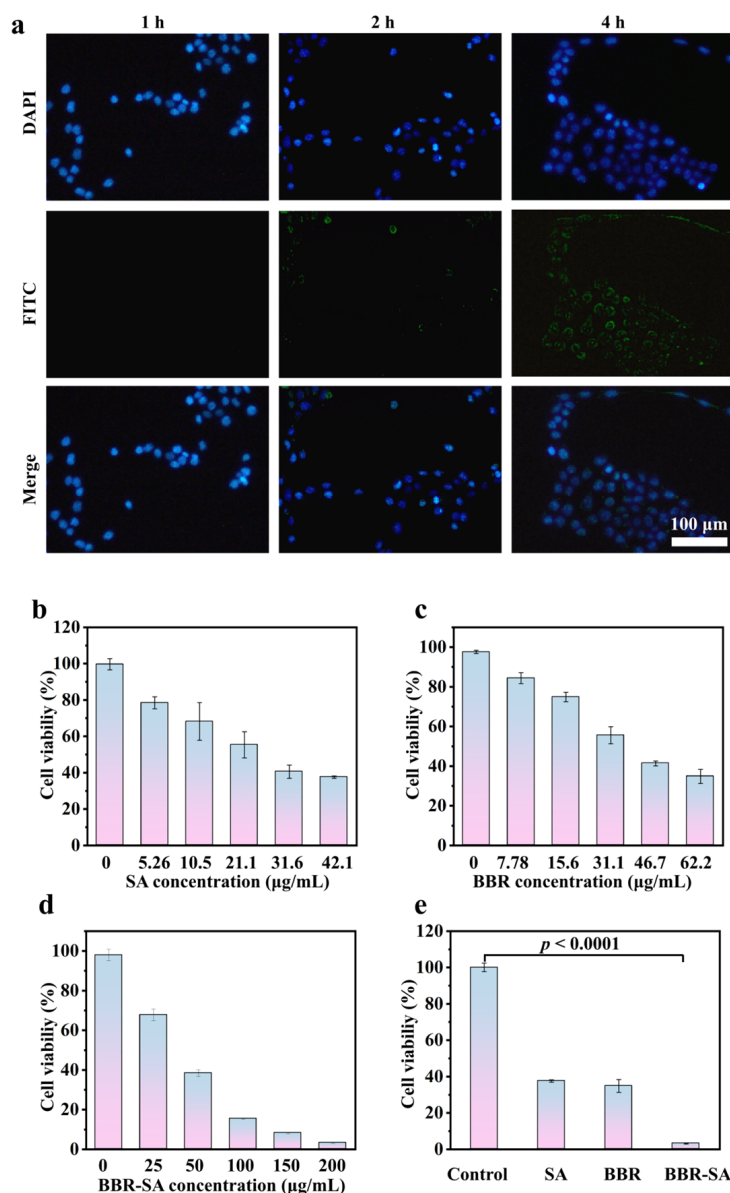


Figure 3. (a) Images of 4T1 cells after incubation with FITC-labeled BBR-SA nanomedicine for 1, 2, and 4 h. Cell viability of 4T1 cells after 24 h incubation with (b) SA, (c) BBR, (d) BBR-SA nanomedicine. (e) Cell viability of 4T1 cells in various groups.

2.3. Cellular Staining Results of BBR-SA Nanomedicine

Subsequently, we employed live/dead staining to visualize cell viability after treatment with BBR-SA nanomedicine. As shown in the Figure 4a, the control group exhibited strong green fluorescence and very weak red fluorescence, confirming that the majority of cells were viable. In the BBR and SA groups, the cells displayed relatively strong green fluorescence along with a certain amount of red fluorescence, indicating that drug treatment had killed a portion of the 4T1 cells. Notably, the green fluorescence was very faint while red fluorescence dominated in the BBR-SA nanomedicine group, suggesting that the majority of 4T1 cells were killed by BBR-SA nanomedicine, which was consistent with the results of CCK-8 assay. Given that 5,5',6,6'-Tetrachloro-1,1',3,3'-tetraethyl-imidacarbocyanine iodide (JC-1) exhibits a shift in fluorescence emission from red to green upon mitochondrial depolarization, this fluorescent dye was employed as an early indicator of apoptosis by monitoring changes in mitochondrial membrane potential. As shown in the Figure 4b, the red fluorescence gradually weakened while the green fluorescence intensified from

control to the BBR, SA, and BBR-SA nanomedicine groups, further demonstrating the potent anti-tumor efficacy of BBR-SA nanomedicine. All the above results confirmed that the synergistic chemotherapeutic effect of BBR-SA nanomedicine is significantly superior to that of individual free drugs. Through the self-assembly of traditional chinese medicine, a synergistic chemotherapeutic effect can be realized.

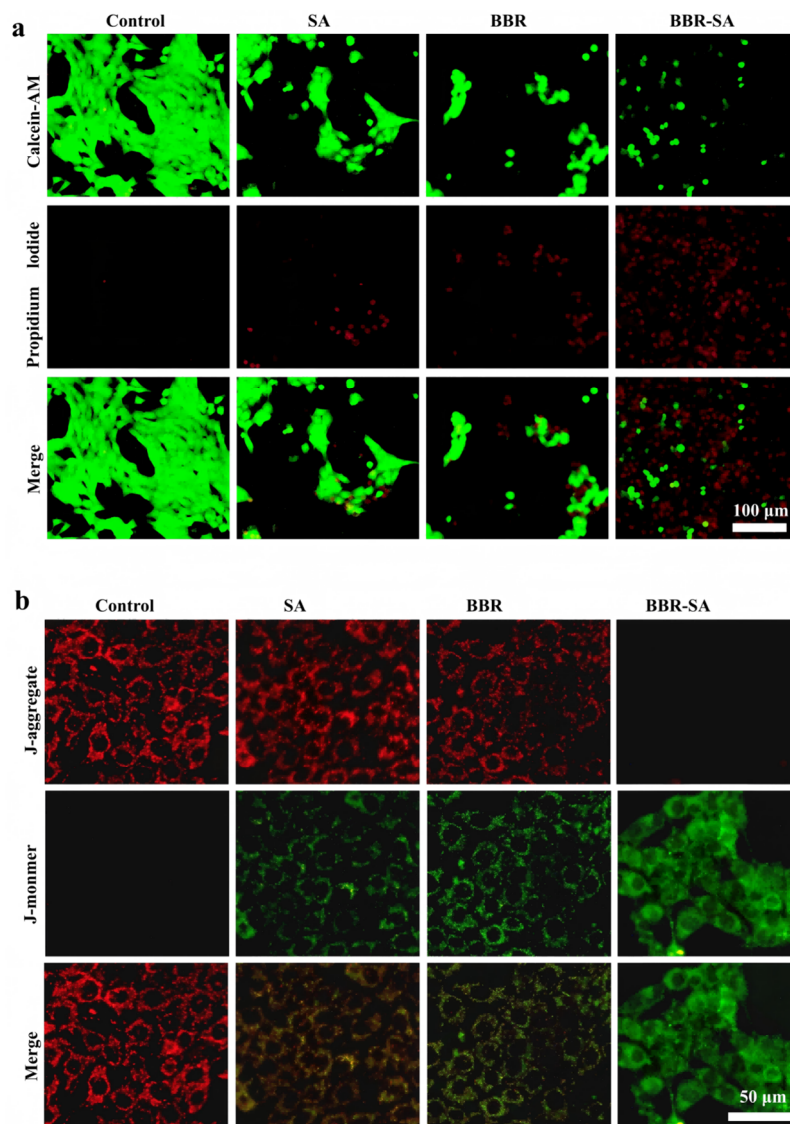


Figure 4. (a) Live/dead staining of 4T1 cells in each group. (b) JC-1 staining of 4T1 cells in each group.

2.4. Anti-Tumor Efficacy of BBR-SA Nanomedicine In Vivo

Given its promising anti-tumor efficacy in vitro, we further investigated its anti-tumor activity in vivo. Firstly, 4T1 cells were inoculating into BALB/c mice to establish murine breast cancer model. When the tumor volume reached approximately 150 mm³, the mice were randomly divided into four groups: control, BBR, SA, and BBR-SA nanomedicine group. The corresponding drugs were administered to each group via tail vein injection. And the tumor volume and body weight were measured every two days during the treatment. In the early stage of treatment, BBR-SA nanomedicine almost completely inhibited tumor growth, whereas BBR and SA groups exhibited certain therapeutic effects but still allowed significant tumor growth. As the treatment continued, the tumor growth trend in the BBR and SA groups became increasingly evident, while the tumor volume in the BBR-SA nanomedicine group remained relatively small (Figure 5a). These results indicated that free

BBR and SA could only partially inhibit tumor growth, whereas BBR-SA nanomedicine significantly enhanced the anti-tumor effect. During this period, the body weight of the mice was also measured. No statistically significant difference in body weight was observed between the BBR-SA nanomedicine group and the control group (Figure 5b). After treatment, mice were euthanized and tumors were excised for photographic assessment. Consistent with prior observations, tumors in the BBR-SA nanomedicine group were markedly smaller than those in the other three groups (Figure S4). Subsequently, hematoxylin-eosin (H&E) staining of the tumor tissues revealed that the BBR-SA nanomedicine group exhibited the poorest tumor tissue density and the most disordered cell arrangement (Figure 5c). In addition, the terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining results revealed the highest number of apoptotic cells in the BBR-SA nanomedicine group (Figure 5d), further confirming its optimal combined chemotherapeutic effect. In conclusion, the BBR-SA nanomedicine prepared through the self-assembly of BBR and SA demonstrated favorable combined chemotherapeutic efficacy *in vivo*.

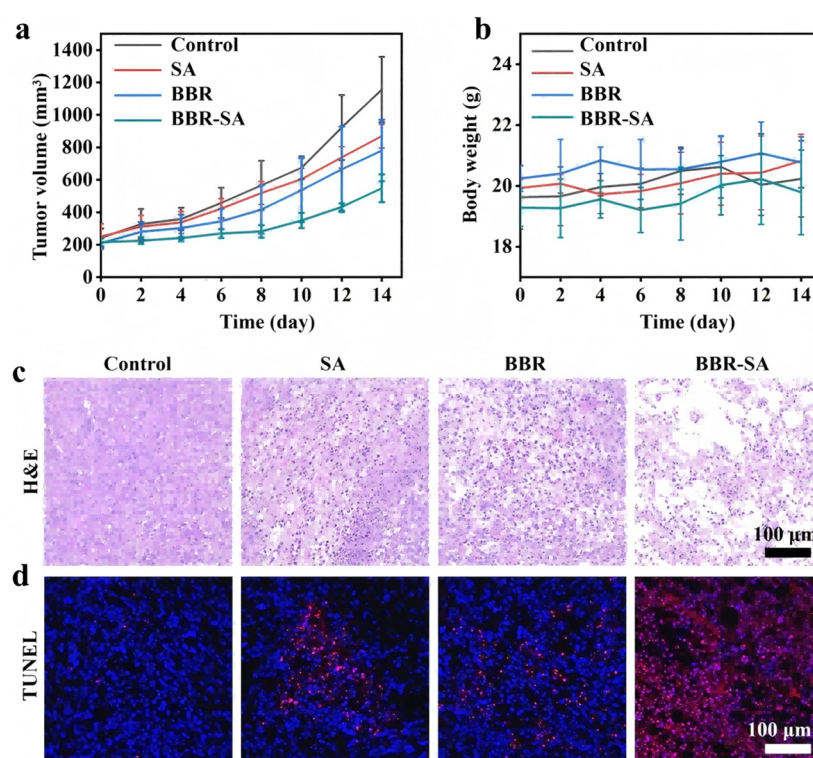


Figure 5. (a) Tumor volume curves in each group. (b) Body weight of mice in each group. (c) H&E staining and (d) TUNEL staining of tumor tissues in each group.

2.5. Potential Toxicity of BBR-SA Nanomedicine

To further investigate its potential toxicity, BBR-SA nanomedicine was intravenously administered to mice. Subsequently, the major organs (heart, liver, spleen, lung, and kidney) were collected and processed for histological staining after 28 days injection. The results indicated that BBR-SA nanomedicine caused no significant toxicity to major organs (Figure 6a). Furthermore, blood index revealed no notable abnormalities between control and BBR-SA nanomedicine groups (Figure 6b–q). These results collectively demonstrated that the BBR-SA nanomedicine not only offer improved therapeutic efficacy compared to free drugs but also exhibited negligible biotoxicity, thereby holding promising potential for development.

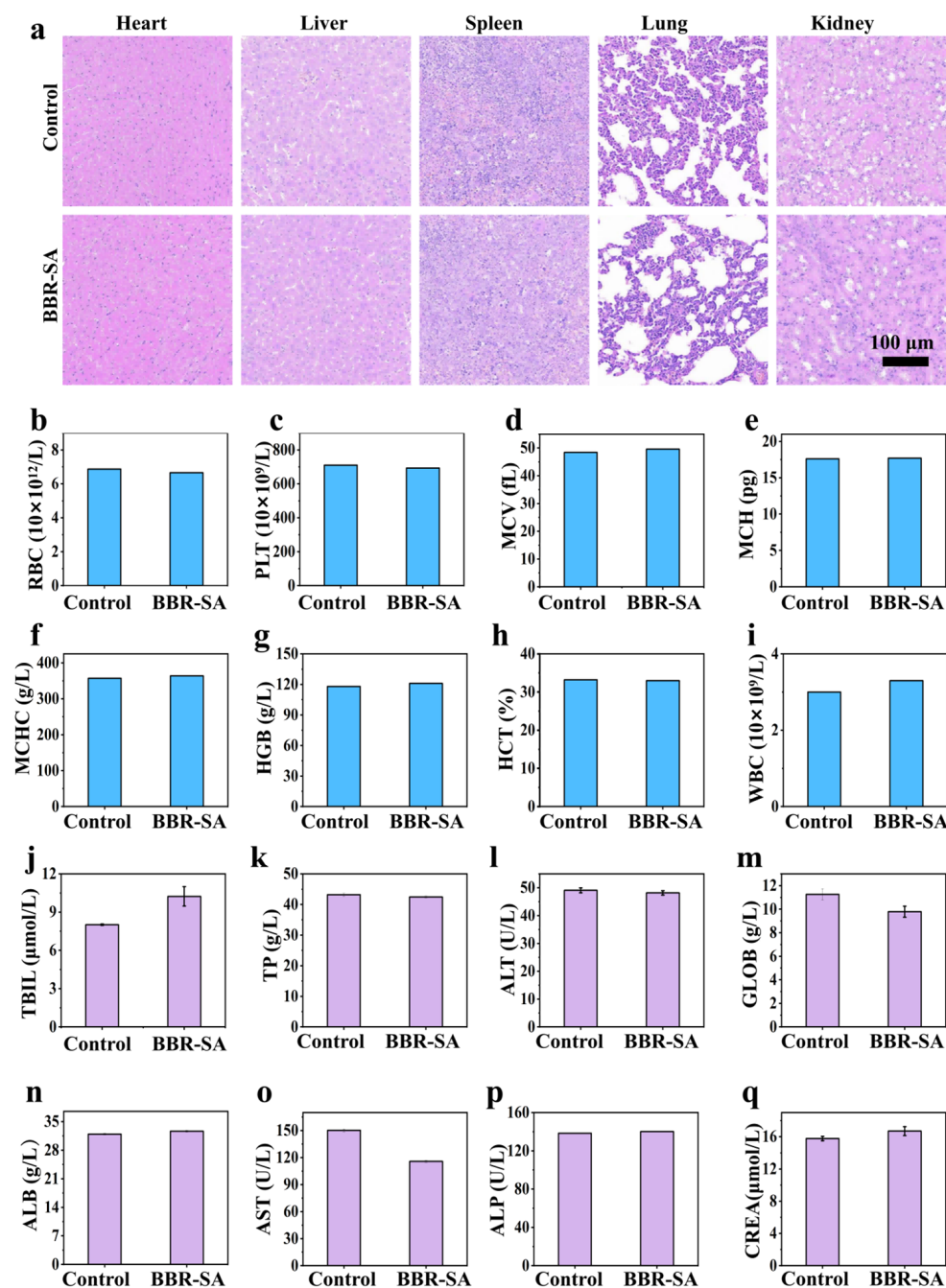


Figure 6. (a) H&E staining of major organs from mice in each group. (b–q) blood index of mice in each group.

3. Materials and Methods

3.1. Materials

Berberine (BBR), sinapic acid (SA), sodium bicarbonate (NaHCO_3), and methanol were purchased from Shanghai Aladdin Biochemical Technology Co., Ltd. (Shanghai, China). The CCK-8 cell counting kit was obtained from Beijing Biosynthesis Biotechnology Co., Ltd. (Beijing, China). Calcein-AM/PI staining reagents were provided by Beijing Solarbio Science & Technology Co., Ltd. (Beijing, China). DAPI staining solution, fluorescein isothiocyanate (FITC) reagent, and JC-1 mitochondrial membrane potential assay kit were purchased from Beyotime Biotechnology Co., Ltd. (Shanghai, China).

3.2. Synthesis of BBR-SA Nanomedicine

BBR-SA nanomedicine were prepared as follows: Firstly, 18 mg SA was dissolved in 1 mL DMSO by ultrasonication and the pH of the solution was adjusted to 7.0–7.5 with NaHCO_3 (5 mg/mL). Then, 27 mg BBR was dissolved in 3 mL methanol by ultrasonication, and this solution was slowly added to the aforementioned mixture under energetic stirring at room temperature. Subsequently, the mixture was slowly introduced into the 10 mL pre-heated PBS (60 °C) and stirred isothermally for 15 min. Finally, the resulting product was dialyzed against PBS for 12 h to obtain BBR-SA nanomedicine.

3.3. Characterization of BBR-SA Nanomedicine

BBR-SA nanomedicine were obtained through the self-assembly of BBR and SA in aqueous solution. Then, its morphology was observed using transmission electron microscopy (TEM). The particle size distribution of BBR-SA nanomedicine in various solvents was determined using a Brookhaven 90Plus PALS Particle Size & Zeta Potential. Zeta potential measurements further elucidated the surface charge characteristics of the BBR, SA, and BBR-SA nanomedicine. Ultraviolet-visible spectroscopy (UV-Vis) confirmed the successful synthesis of BBR-SA nanomedicine. Furthermore, fourier transform infrared spectroscopy (FT-IR) was employed to investigate the interaction mechanism between BBR and SA during the self-assembly process.

3.4. Cell Culture

Mouse embryonic fibroblast cells (3T3) and mouse mammary carcinoma cells (4T1) were cultured in 1640 medium supplemented with 10% FBS and 1% penicillin-streptomycin. All cells were maintained at 37 °C with 5% CO_2 .

3.5. Cellular Uptake of BBR-SA Nanomedicine

4T1 cells were seeded in a 96-well plate and incubated overnight. After removing the existing culture medium, the cells were treated with FITC-labeled BBR-SA nanomedicine, followed by incubation for 1, 2, and 4 h, respectively. Then, the cells were stained with DAPI and fixed with 4% paraformaldehyde (PFA). Finally, cellular imaging was performed using an inverted fluorescence microscope.

3.6. Cytotoxicity of BBR-SA Nanomedicine

4T1 cells were seeded in 96-well plates and incubated at 37 °C with 5% CO_2 . Then, SA (0, 5.26, 10.5, 21.1, 31.6, 42.1 $\mu\text{g/mL}$), BBR (0, 7.78, 15.6, 31.1, 46.7, 62.2 $\mu\text{g/mL}$), and BBR-SA nanomedicine (0, 25, 50, 100, 150, 200 $\mu\text{g/mL}$) were added into 96-well plates and incubated for 24 h, respectively. Subsequently, CCK-8 reagent was added and further incubated for 2 h. Finally, the fluorescence at 450 nm was measured using a microplate reader.

3.7. Cell Staining Assay

4T1 cells were plated in a 96-well plate and treated with BBR, SA, or BBR-SA nanomedicine for 24 h. Then, Calcein-AM working solution was added to the wells and incubated at 37 °C for 20 min in the dark, followed by PI staining solution for an additional 5 min. Fluorescence images were acquired using a fluorescence microscope. The JC-1 staining procedure was identical to that used for Calcein-AM/PI staining, with the exception that JC-1 dye was replaced.

3.8. Anti-Tumor Effect of BBR-SA Nanomedicine In Vivo

Firstly, forty female BALB/c mice were used to establish a subcutaneous tumor model via implantation of 4T1 tumor cells. When the tumor volume reached approximately 150 mm^3 , the mice were randomly assigned into the following groups: control,

BBR, SA, and BBR-SA nanomedicine. Each group received intravenous injections of the corresponding drugs via the tail vein every other day. Throughout the treatment period, body weight was recorded every other day, and tumor dimensions (length L and width W in mm) were measured using calipers. Tumor volume was calculated as $V = L \times W^2/2$. At the end of the treatment protocol, all remaining mice were euthanized, and tumor tissues were excised for therapeutic evaluation.

3.9. Long-Term Toxicity of BBR-SA Nanomedicine

Twenty female Balb/c mice were selected and randomly divided into two groups, receiving tail vein injections of normal saline and BBR-SA nanomedicine, respectively. After 28 days, one mouse from each group was randomly selected and euthanized by cervical dislocation. The major organs (heart, liver, spleen, lungs, kidneys) were dissected for histological section analysis. Additionally, blood was collected from all mice in each group via retro-orbital bleeding. Half of the blood samples were used for hematological tests, while the other half were allowed to stand for 1 h before centrifugation to obtain the supernatant for blood biochemical analysis.

4. Conclusions

In this essay, a novel nanomedicine (BBR-SA) was conducted based on the self-assembly of BBR and SA for synergistic chemotherapy. According to the study, the self-assembly of BBR and SA is mainly driven by π - π interactions, electrostatic forces, and hydrogen bonds. Moreover, the prepared BBR-SA nanomedicine exhibited high drug-loading capacity and favorable water dispersibility. Furthermore, BBR-SA nanomedicine demonstrated markedly enhanced therapeutic efficacy over free drugs, as evidenced by both in vitro cytotoxicity assays and in vivo studies using a murine breast cancer model, underscoring the potential of self-assembled nanomedicine for synergetic chemotherapy. Importantly, no significant biotoxicity was observed after 28 days treatment with BBR-SA nanomedicine. Therefore, the BBR-SA nanomedicine developed in this study represent a safe, biocompatible, and highly efficient strategy for breast cancer treatment.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules31040621/s1>, Figure S1: The standard absorption curve of SA; Figure S2: The standard absorption curve of BBR; Figure S3: Cell viability of 3T3 cells after 24 h incubation with BBR-SA nanomedicine; Figure S4: Photographs of dissected tumors in each group.

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Institutional Review Board Statement: The animal study protocol was approved by the Animal Management and Ethics Committee of Henan University of Traditional Chinese Medicine (approval number IACUC-202412015).

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no competing financial interests.

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