

# Biomimetic Copper-Doped Polypyrrole Nanoparticles for Enhanced Cancer Low-Temperature Photothermal Therapy

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**Introduction:** Photothermal therapy (PTT) has a significant potential for its application in precision tumour therapy. However, PTT-induced hyperthermia may damage healthy tissues and trigger the expression of heat shock proteins (HSPs), thereby compromising the long-term therapeutic efficacy of PTT.

**Methods:** In this study, a biomimetic drug delivery system comprising CuP nanozymes as the inner core and platelet membrane (PM) as the outer shell was successfully developed for administering synergistic chemodynamic therapy and mild PTT. PM is encapsulated on CuP to form this biomimetic nanoparticle (PM-coated CuP nanoparticles, PC). PC possesses peroxidase (POD) activity, can facilitate the conversion of hydrogen peroxide into  $\cdot\text{OH}$ , thereby inhibiting the expression of HSPs.

**Results:** Upon exposure to low-power laser irradiation ( $0.5 \text{ W/cm}^2$ , 1064 nm), PC can convert near-infrared II laser energy into heat energy, thereby enabling the administration of enhanced mild PTT. In vitro and in vivo experiments have demonstrated that this synergistic approach can induce over 90% tumour eradication with favourable biocompatibility.

**Discussion:** PC exhibits high efficacy and biocompatibility, making it a promising candidate for future applications.

**Keywords:** biomimetic nanoparticles, copper-doped polypyrrole nanoparticles, low-temperature photothermal therapy

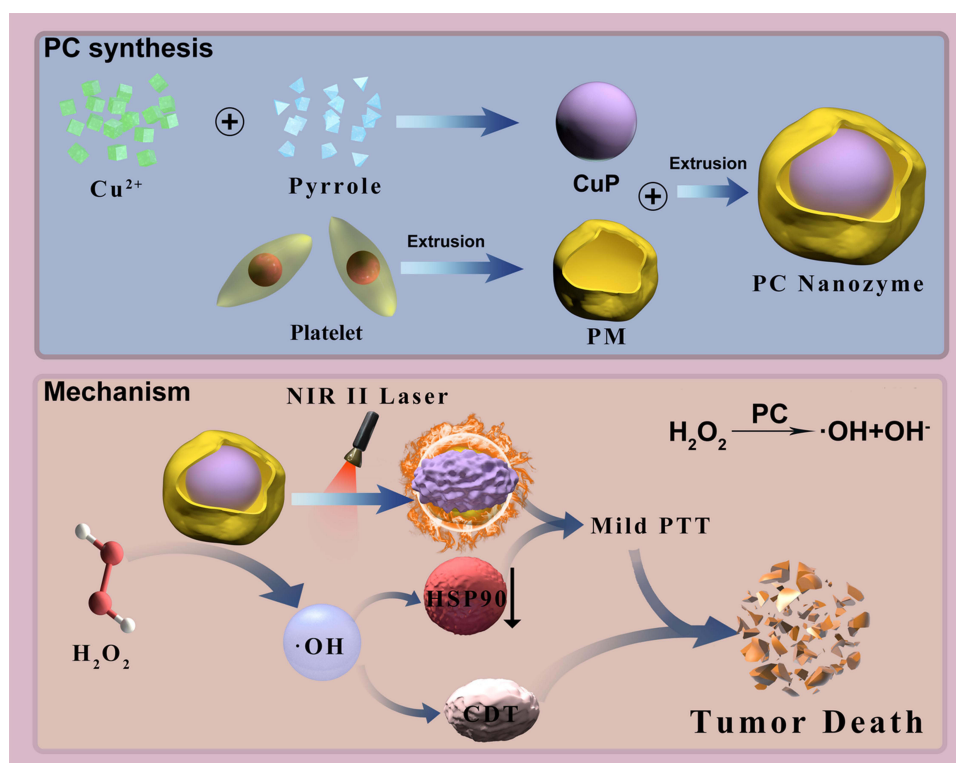
## Introduction

Photothermal therapy (PTT) is a method to treat cancers using near-infrared light (NIR).<sup>1,2</sup> PTT kills tumour cell by converting the absorbed light energy into heat energy upon the irradiation of the photothermal agent (PTA) with a near-infrared laser to ablate the tumour.<sup>3-5</sup> PTT has great potential for clinical application owing to its several advantages, including its non-invasive nature, few adverse reactions and low systemic toxicity, and it has become a highly popular cancer treatment method.<sup>6,7</sup> For complete tumour ablation, high-temperature PTT ( $>50^\circ\text{C}$ ) is often used to induce complete cell necrosis.<sup>8</sup> However, hyperthermia and high-intensity laser irradiation associated with this approach inevitably damage nearby healthy tissues.<sup>9</sup> In addition, PTT can activate the heat shock response, which exerts cell-protective and anti-apoptotic effects, and induce the overexpression of heat shock proteins (HSPs).<sup>10</sup> HSPs participate in the development of instantaneous heat resistance and acquisition of permanent heat resistance, thereby enhancing the heat resistance of tumour cells and helping them to resist PTT.<sup>9</sup> HSP 90 and HSP 70 proteins, which belong to the HSPs family, can help cancer cells fight against harsh environment, repair cell damage caused by photothermal therapy and improve their survival.<sup>11</sup>

As messengers of cell injury, reactive oxygen species (ROS) can cause extensive cell damage by oxidising cell membranes and destroying proteins and DNA.<sup>12–26</sup> Excessive ROS production is associated with many forms of apoptosis and necrosis.<sup>15,17,19,20,27,28</sup> Studies have confirmed a correlation between ROS production and HSPs induced expression.<sup>11</sup> HSP 70 plays a similar role to small molecular heat shock protein in the process of resisting oxidative stress. And HSP 90 in mouse tissues and cells can resist heat-induced apoptosis by inhibiting ROS induction.<sup>29</sup> Active cysteine present on the surface of HSP 90 can reduce level, indicating the crucial role of HSP 90 in regulating cellular redox balance.<sup>30</sup> Nanozymes can leverage the enhanced permeability and retention effect exerted by solid tumours to target tumour sites. Additionally, they initiate catalytic reactions in response to the weak acidity, low oxygen levels and high  $\text{H}_2\text{O}_2$  concentration in the tumour microenvironment.<sup>5,14,31</sup> Consequently, nanozymes consume endogenous substances such as glutathione (GSH) or catalyse  $\text{H}_2\text{O}_2$  to produce highly toxic  $\cdot\text{OH}$ , which disrupts the redox steady state and ultimately inhibits HSPs expression. Furthermore, inorganic nanozyme has more stable structure, cost-effective preparation and preservation processes, versatile functionality, adjustable catalytic activity and better biocompatibility and safety than natural enzymes.<sup>32</sup> Consequently, they can be used along with PTT to achieve superior therapeutic effects.

Currently, the traditional nanomaterial-based delivery systems have poor biocompatibility. After entering the body, drugs and carriers are easily captured and removed in the process of blood circulation by the reticular endothelial system, which comprises mononuclear macrophages in systemic circulation. This results in a short blood circulation time that considerably hampers their effectiveness. In addition, as nanomaterials lack active targeting abilities, they are widely distributed throughout the body can easily cause systemic toxicity.<sup>33</sup> Platelets are important circulating cells in the body that have been widely used in constructing bionic drug delivery systems.<sup>27,33,34</sup> Platelets have many advantages over other cells. First, platelets can specifically adhere to bleeding and injury sites.<sup>33,35,36</sup> Second, platelet membranes (PMs) can produce a “do not eat me” signal through the CD47 receptor on their surface, thus evading elimination by phagocytes.<sup>37</sup> Due to the expression of specific tumour-related receptors and proteins, PM-coated nanomaterials can accurately target tumour cells. P-selectin on the surface of PMs can recognise the CD44 receptor on the surface of tumour cells, enabling platelets to target various tumour cell lines.<sup>38,39</sup>

Here, we designed PM-coated CuP nanoparticles (named PC) that can be selectively delivered to the tumour site to overcome the heat resistance of tumour cells to achieve efficient and mild PTT (Scheme 1). To reliably synthesise CuP,



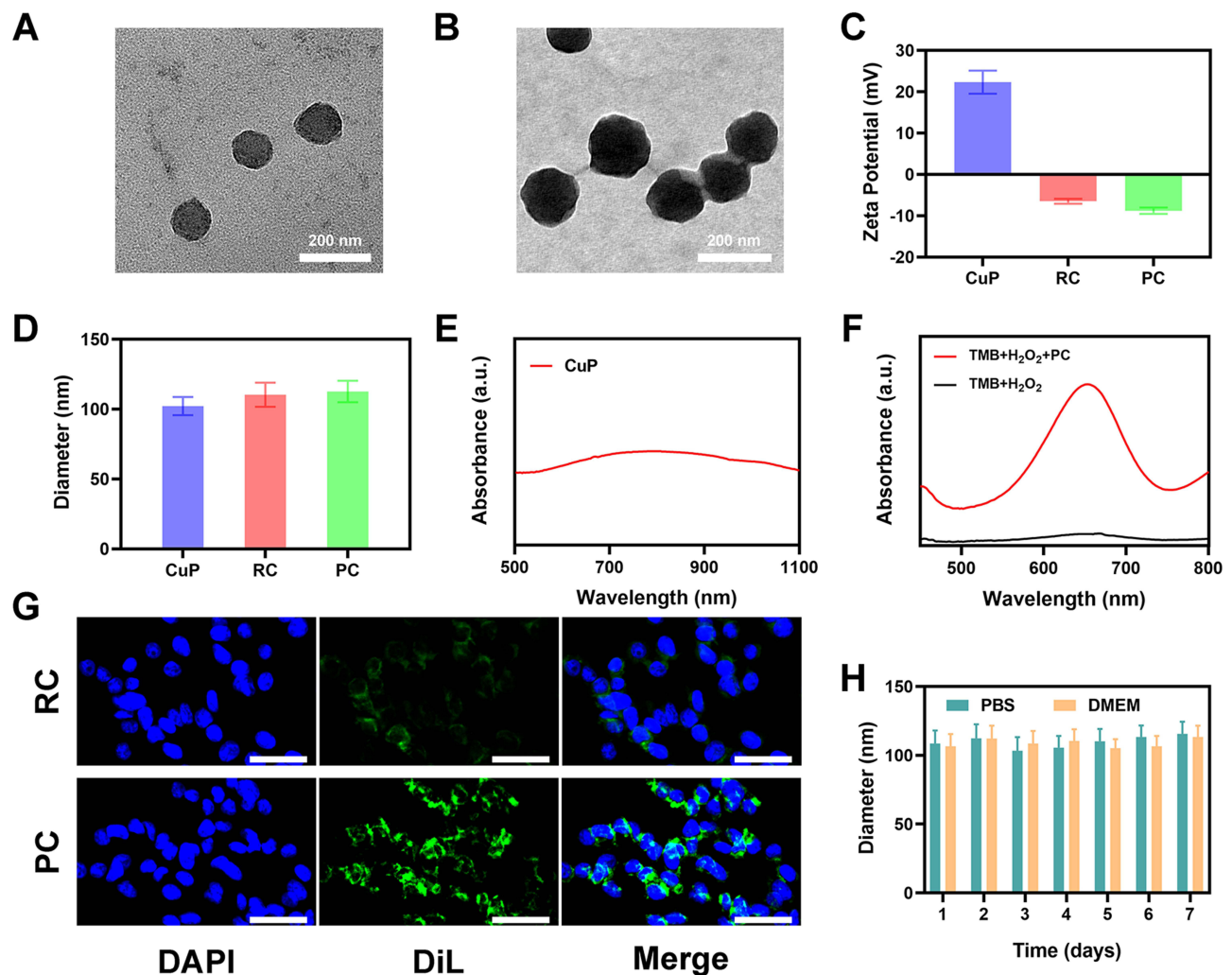
**Scheme 1** Schematic illustration of biomimetic Cu-doped polypyrrole nanoparticles for enhanced cancer low-temperature PTT.

CuCl<sub>2</sub> was used as an oxidation catalyst. Polyvinyl alcohol (PVA) was used as a stabiliser during the growth of polypyrrole to achieve reliable synthesis of CuP. CuP converts light energy into heat energy in response to near-infrared II (NIR-II) laser irradiation and catalyses high level of H<sub>2</sub>O<sub>2</sub> in the tumour microenvironment to produce highly toxic ·OH that kills tumour cells. In addition, PM coating increases the circulation time of PC nanoparticles in vivo and their accumulation at tumour sites. More importantly, CuP with peroxidase-like activity inhibits HSP 90 expression, thus reducing the heat resistance of cells, overcoming the photothermal resistance of tumour cells and greatly enhancing the effect of CuP-mediated mild PTT. Both in vivo and in vitro results showed that PC in conjunction with the NIR-II laser achieves a favourable tumour-killing effect and has a good biological safety. The tumour-targeted mild PTT in the NIR-II region provides more opportunities for the successful clinical application of PTT.

## Results and Discussion

### Preparation and Characterization of CuP Nanozymes

We synthesised CuP nanozymes from pyrrole, CuCl<sub>2</sub> and PVA.<sup>40</sup> The transmission electron microscopy (TEM) image shown in Figure 1A showed the structure of spherical CuP, and the image in Figure 1B showed the PM-coated CuP (PC). A membrane coating was observed on the surface of CuP, confirming the successful coating of PM. Elemental EDS-



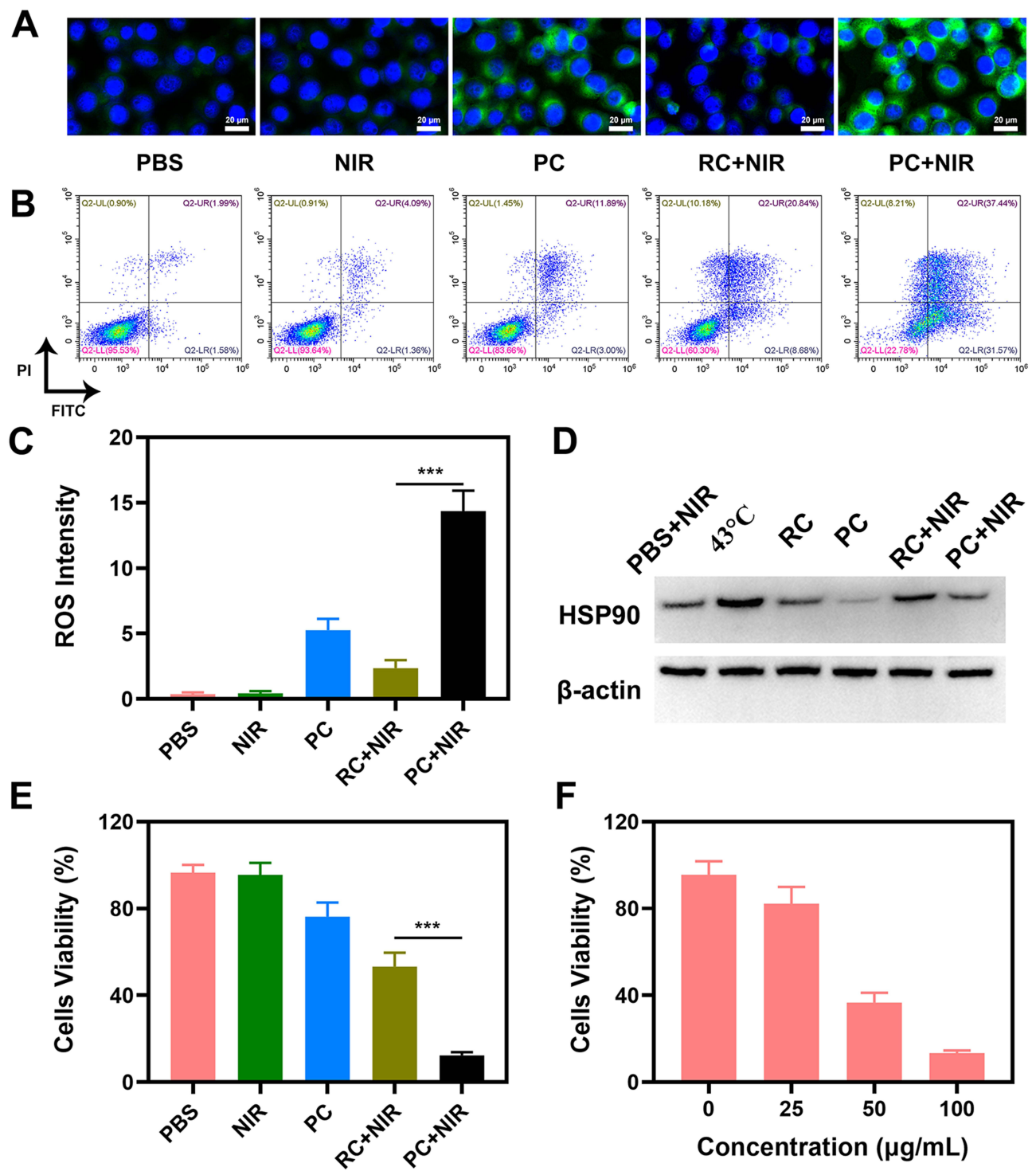
**Figure 1** Characterisation of PC. (A) TEM image of CuP. (B) TEM image of PC nanozymes. (C) Zeta potential of CuP, RC and PC. Software: GraphPad Prism 6. (D) Hydrodynamic diameter of CuP, RC and PC. Software: GraphPad Prism 6. (E) Absorbance spectra of CuP. Software: GraphPad Prism 6. (F) UV/vis absorbance spectra and colour changes of TMB in different reaction systems. Software: GraphPad Prism 6. (G) Targeting ability of RC and PC for cancer cells. Blue: CT26 cell nucleus; green: DiI-labelled RC or PC. Scale Bar: 50  $\mu$ m. (H) Hydrodynamic diameter changes in PC dispersed in different physiological media at different time points. Software: GraphPad Prism 6.

mapping images of PC was shown in [Figure S1](#). The FTIR results was shown in [Figure S2](#). The peaks located in the range of 1710–1750  $\text{cm}^{-1}$  may be related to the amide bonds of proteins, while the peaks located in the range of 2920–2850  $\text{cm}^{-1}$  may be related to the methyl and methylene bonds of phospholipids. The peak located near 1540–1550  $\text{cm}^{-1}$  is related to the amide bond vibration of the protein. We measured the zeta potential of CuP before and after PM coating and compared both values with CuP loaded on the red cell membrane (RC), which lacked active targeting ability. The results showed that the surface zeta potential of CuP changed from 20 mV to  $-6$  mV after co-extrusion with the erythrocyte membrane, and the zeta potential of PC also considerably decreased ([Figure 1C](#)). In addition, the particle size was measured using dynamic light scattering ([Figure 1D](#)). The sizes of RC and PC were slightly larger than that of CuP. We measured the particle size of PC incubated in different physiological media (PBS and DMEM) for a week, and the results showed that PC had good stability ([Figure 1H](#)).  $\text{Cu}^{2+}$  release from PC under different  $\text{H}_2\text{O}_2$  condition was shown in [Figure S3](#). The results indicated that copper ions can be slowly released from PC under the presence of hydrogen peroxide. Currently, most photothermal treatments focus on the first NIR (NIR-I) biowindow (750–1000 nm). However, the second NIR (NIR-II) biowindow (1000–1350 nm) has the advantages of having a larger maximum permissible exposure and deeper laser penetration than those of NIR-I. The UV/vis-NIR absorption spectrum showed that CuP had a broad absorption band at 1000–1100 nm, indicating its suitability for its use as NIR-II PTA ([Figure 1E](#)). Photothermal stability is a crucial aspect to assess PTAs. To further study the photothermal characteristics of PC, it was irradiated with a 1064-nm laser ( $0.5 \text{ W/cm}^2$ ) and the temperature curve was observed. The temperature of PC increased by approximately  $24^\circ\text{C}$  in 5 min. Next, the laser was turned off to allow the recovery of the initial temperature. This cycle was repeated thrice ([Figure S4](#)). The photothermal effect of PC exhibits concentration dependence ([Figure S5](#)). The results confirmed the stable photothermal performance of the PC. Using TMB as a chromogenic substrate, absorption curves of different treatment groups were measured to verify the POD activity of PC. As shown in [Figure 1F](#), almost no peak change was observed after TMB was incubated with  $\text{H}_2\text{O}_2$ . However, a characteristic peak was produced at 652 nm after PC was added, indicating that PC can catalyse  $\text{H}_2\text{O}_2$  to produce  $\cdot\text{OH}$ . Although the coating of erythrocyte membrane can prolong the circulation time of nanomaterials, it lacks targeting ability. In addition, studies have shown that copper ions can also generate hydroxyl radicals through the Fenton reaction.<sup>40,41</sup> The free radicals generated by PC may partially come from the released copper ions. To verify the active targeting ability of PC, DiI-labelled PC and RC were incubated with CT26 cells. Confocal laser scanning microscopy (CLSM) results showed a small number of RC entered the cells, whereas the PC group showed bright fluorescence, indicating its active targeting ability ([Figure 1G](#)). Thus, the suitability of PC as an ideal platform for actively targeted tumour cells was further validated by these experimental data.

## In vitro Anti-Tumor Study

To further confirm  $\cdot\text{OH}$  production at the cellular level, we used DCFH-DA as a fluorescent probe to detect intracellular  $\cdot\text{OH}$  levels in different treatment groups using CLSM imaging ([Figure 2A](#) and [C](#)). The combination of PC with low-power NIR-II laser irradiation (PC+NIR) produced the strongest green fluorescence among all groups. This result showed that the photothermal conversion caused by PC under 1064-nm laser irradiation can greatly promote the production of  $\cdot\text{OH}$  radicals. The quantitative results of ROS were consistent with those of fluorescence intensity. We used an FITC-PI apoptosis kit to study the apoptosis of CT26 cells in different treatment groups ([Figure 2B](#)). Compared with the PBS group, apoptosis was not observed in the NIR group, indicating that low-power laser treatment alone had a limited effect on cell killing. The PC group achieved a certain degree of cell killing, whereas the RC+NIR group moderately inhibited cell viability, with approximately 60.3% cell viability. Notably, the PC+NIR group achieved the highest degree of apoptosis among all groups, where 31.57% and 37.44% of cells were in the early and late apoptosis stages, respectively. These results showed that the cytotoxicity of PC and NIR alone was weak, while PC+NIR achieved the effect of  $1 + 1 > 2$ . HSPs expression (HSP 90) was detected using Western blot analysis to verify the relationship between intracellular ROS and mild PTT. The bands shown in [Figure 2D](#) showed the expression level of HSP 90 in the different treatment groups. At  $43^\circ\text{C}$ , the expression of HSP 90 in cells was considerably high in all cells, but its expression was low in PC-treated cells. This observation confirmed that PC can reduce the heat tolerance of tumour cells and promote apoptosis. Furthermore, the cell counting kit-8 was used to detect cell viability in the treatment groups to study the photothermal anti-tumour effect of PC combined with the 1064-nm laser ( $0.5 \text{ W/cm}^2$ ) in vitro ([Figure 2E](#) and [F](#)). Consistent with the





**Figure 2** The PC showed synergistic anti-tumour ability in the in vitro experiments. (A) Confocal images of DCFH-DA in CT26 cells after treatment with different formulations. (B) Representative flow cytometry plots after the annexin V-FITC/PI staining of CT26 cells. (C) ROS fluorescence intensity after the indicated treatments. (D) Western blot analysis of HSP 90 after the indicated treatments. (E) Cell viability of CT26 cells cultured in the presence of various formulations. (F) Cell viability of CT26 cells cultured in the presence of PC+NIR (PC concentration: 0, 25, 50 and 100 µg/mL). Significant differences among groups as calculated using the Student's t-test. \*\*\* $p < 0.005$ . Software of Figure 2C–F: GraphPad Prism 6.

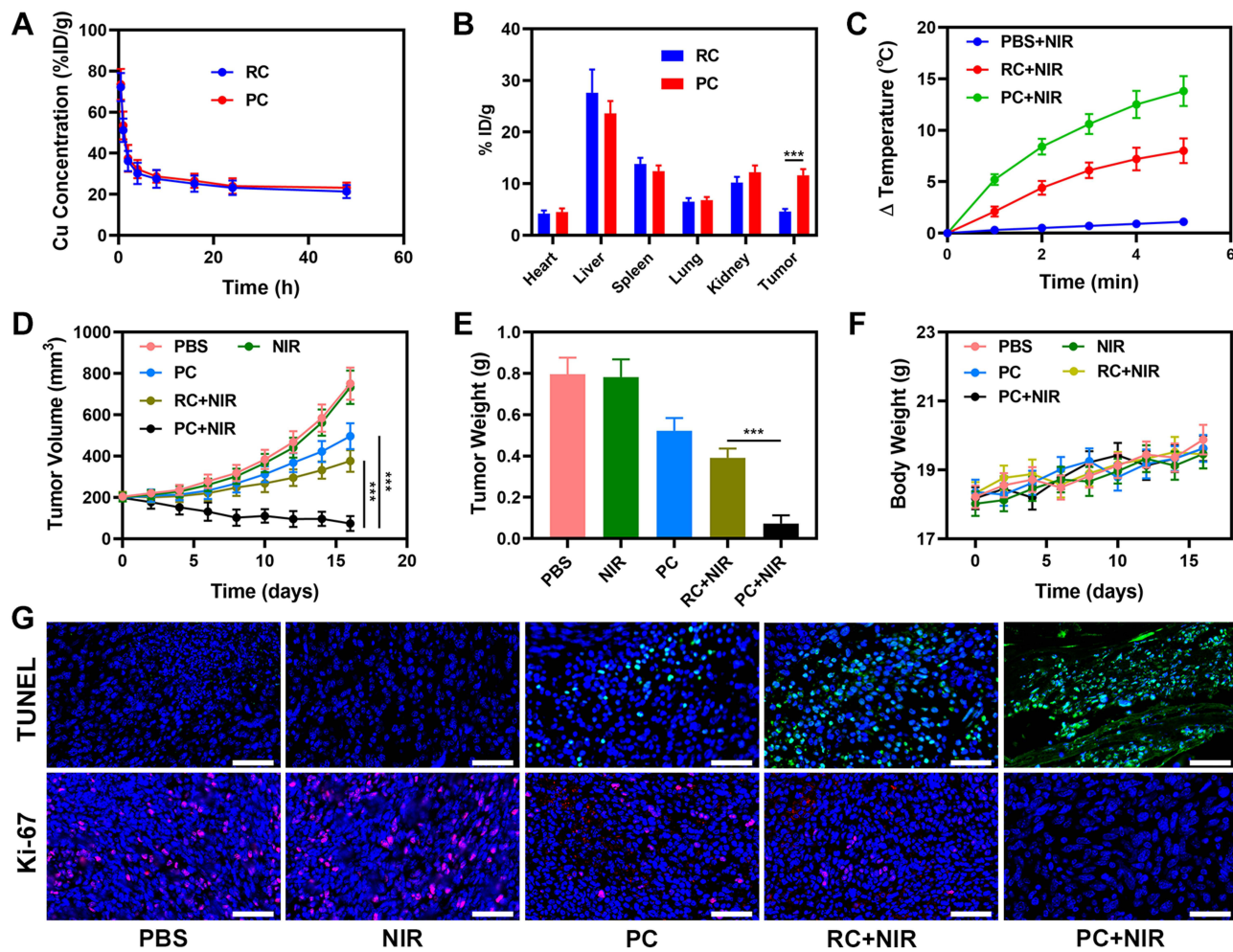
previous results, the PC+NIR group showed the best cell viability inhibition effect among all groups. Notably, the PC+NIR group exhibited significant differences in cell viability compared with the RC+NIR group. This disparity may be attributed to the fact that PM coating allowed more CuP nanozymes to be phagocytised by tumour cells. Consequently, CuP catalysed intracellular  $H_2O_2$  to produce a large number of ROS, thereby disrupting redox homeostasis, inhibiting

HSPs activity and enhancing the effectiveness of PTT. After irradiation, the cell viability of the PC treatment group showed a decreasing trend with increasing PC concentration. Overall, the in vitro cell experiments showed that our designed PC nanozyme can achieve improved tumour cell-killing ability when used in combination with NIR-II laser irradiation.

## In vivo Anti-Tumour Study

The prerequisite for effectively treating tumours using nanomaterials is having the ability to achieve high enrichment efficiency in tumour sites. Considering that the tumour cell membrane can improve the cell uptake and targeting efficiency of PC in vitro, we initially studied the uptake ability of PC and RC in subcutaneous tumours of CT26 tumour-bearing mice. Pharmacokinetic experiments showed that both PC and RC groups achieved good long-term circulation (Figure 3A). An in vivo biological distribution experiment showed that RC and PC mainly accumulated in the liver. However, RC exhibited lower accumulation at the tumour site than PC, confirming the active targeting ability of PM in vivo (Figure 3B). In platelets, the CD44 protein targeted tumour cells through the P-selectin protein on the surface. As a critical PM protein, P-selectin plays an important role in tumour targeting.<sup>34,35,42</sup>

Photothermal imaging technology was used to evaluate the photothermal conversion performance of PC in vivo. After injecting different formulations into CT26 tumour-bearing mice through the tail vein for 12 hours, the temperature



**Figure 3** In vivo anti-tumour capability analysis. (A) Pharmacokinetic behaviour of RC and PC. (B) Quantitative analysis of Cu biodistribution in tissues and tumours of tumour-bearing mice injected with RC and PC. (C) Temperature change of the tumour upon laser irradiation. (D) Relative changes in tumour volume in mice after the indicated treatments. (E) Evolution of the tumour weight during therapy. (F) Changes in the body weight of the mice recorded every other day after the indicated treatments. (G) TUNEL and Ki-67 staining of tumour sections from the tumour-bearing mice. Scale bars:50 $\mu$ m. Significant differences among the groups as calculated using the Student's *t*-test. \*\*\**p* < 0.005. Software of Figure 3A–F: GraphPad Prism 6.

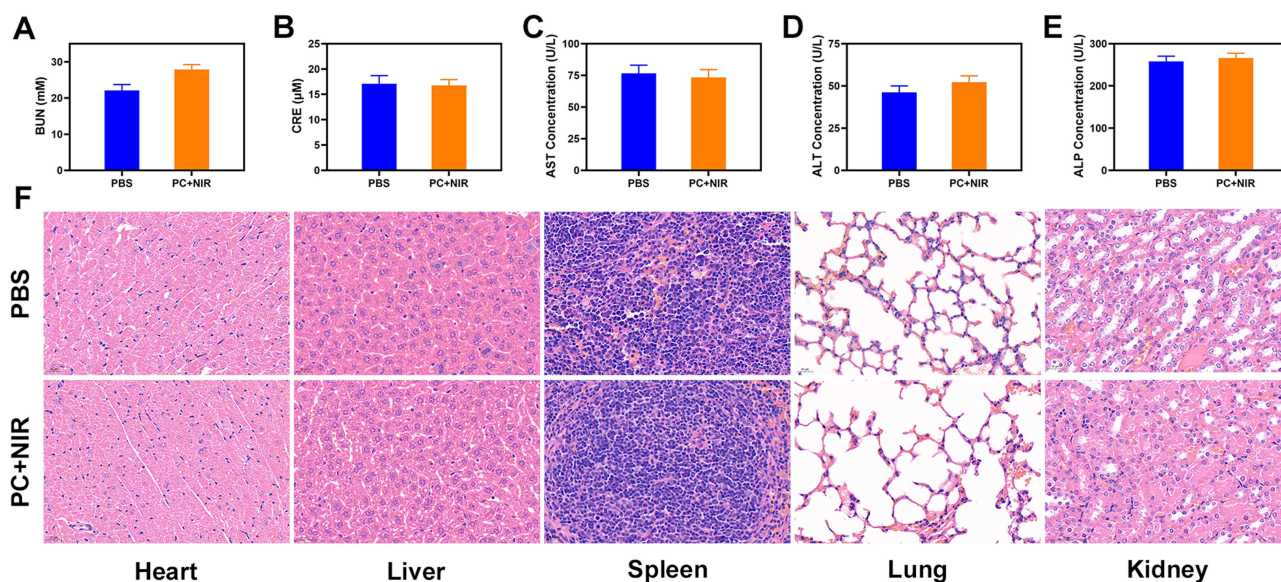
change at the tumour site was recorded using an infrared thermal imager under 1064-nm laser irradiation. The temperature of the PBS+NIR group barely increased over time, while that of the PC+NIR group increased significantly, rising by approximately 13.8°C within 5 min (Figure 3C), indicating the considerable potential for achieving a PTT effect in tumour treatment. Next, we investigated the anti-tumour effect of PC-mediated PTT *in vivo*. The CT26 tumour-bearing mice were randomly divided into five groups: (1) PBS, (2) NIR, (3) PC, (4) RC+NIR and (5) PC+NIR. The tumour size and body weight of the mice were measured every 2 days after administering different treatments.

The tumour volume increased rapidly in the PBS and NIR groups; however, the tumour volume in the PC group showed slight growth stagnation (Figure 3D). The tumour volume of the RC+NIR group gradually increased in the first week and then slowly increased in the following week, indicating a moderate treatment effect. Notably, the tumour volume curve of the PC+NIR group decreased steadily over time, suggesting that the PC nanozyme achieved efficient mild PTT, thus inhibiting tumour growth. After the treatment, tumour tissues of each group were imaged and weighed and the average weight of tumour tissues was compared across different treatment groups (Figures S6 and S7). As shown in Figure 3E, the tumour weight of the PC+NIR group significantly differed from that of the other groups, which confirmed that PC+NIR group had a stronger tumour inhibition effect. Furthermore, we monitored changes in the weight of mice in the different treatment groups. During the treatment, the weight of mice in each group did not change considerably but increased slowly, indicating that our treatment method had no obvious toxicity *in vivo* (Figure 3F).

To further study the mechanism underlying tumour tissue destruction in the CH+NIR group, we stained the tumour tissue to detect proliferation and apoptosis signals after the treatment (Figure 3G). TUNEL staining showed that the PC+NIR group induced the best apoptosis among all groups. The image of tissues stained with Ki-67, an antigen related to cell proliferation, showed that the expression of Ki67 protein in the PC+NIR group was remarkably reduced. This result proves that combining PC and NIR can enhance cancer treatment.

## Biosafety Assessment

In addition, we conducted further tests to evaluate the impact of PC on the blood biochemical indexes of the PC+NIR group. Figure 4A–E showed that the indexes of mice were within the normal range, confirming that the safety of the treatment. After the treatment, main organs (heart, liver, spleen, lung and kidney) of the mice were stained with hematoxylin and eosin (H&E). Histological analysis of H&E staining results showed no obvious pathological changes



**Figure 4** Result of *in vivo* safety experiments. (A–E) Blood biochemistry data showed kidney and liver function markers (BUN, CRE, AST, ALT and ALP) after various treatments. (F) Histopathological analysis results from H&E-stained images of major organs, including heart, lung, liver, kidneys and spleen of mice, which were exposed to different treatments 16 days post-injection under laser irradiation. Software of Figure 4A–E: GraphPad Prism 6.



in the PC group, even under NIR laser irradiation (Figure 4F), which indicated that the biological safety of PC in vivo was acceptable.

## Conclusions

In this study, a biomimetic nanozyme system (termed “PC”) was designed to enable the administration of mild PTT. PM coating significantly prolonged the blood circulation time of PC while enabling PC to achieve tumour targeting. PC, which possessed POD activity, catalysed intracellular H<sub>2</sub>O<sub>2</sub> to generate abundant ·OH and consequently induce tumour cell death. Additionally, this process inhibited the expression of HSP 90, thereby reducing the thermal tolerance of tumour tissues and enhancing the effectiveness of mild PTT under the irradiation of a 1064-nm laser with low power density. In addition, this treatment approach showed good biological safety, with no noticeable abnormalities in any of the treatment groups. Thus, this system can be used as a novel strategy for enhancing mild photothermal tumour therapy.

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## Disclosure

The authors report no conflicts of interest in this work.

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