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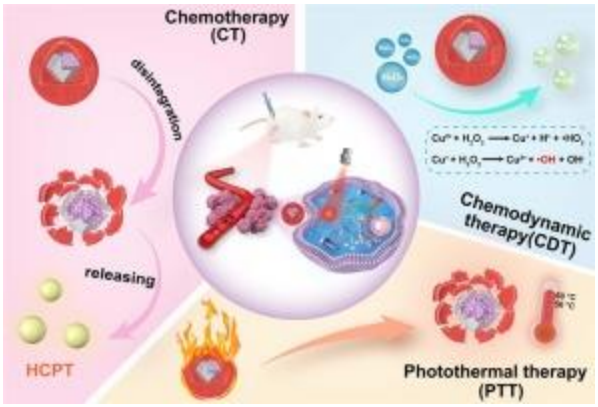
Abstract

Nanoformulations for combining chemotherapy, chemodynamic therapy, and photothermal therapy have enormous potential in tumor treatment. Coating nanoformulations with cell membranes endows them with homologous cellular mimicry, enabling nanoformulations to acquire new functions and properties, including homologous targeting and long circulation *in vivo*, and can enhance internalization by homologous cancer cells. Herein, we fused multifunctional biomimetic nanoformulations based on Cu-doped zeolitic imidazolate framework-8 (ZIF-8). Hydroxycamptothecin (HCPT), a clinical anti-tumor drug, was encapsulated into ZIF-8, which was subsequently coated with polydopamine (PDA) and red blood cell membrane. The as-fabricated biomimetic nanoformulations showed an enhanced cell uptake *in vitro* and the potential to prolong blood circulation *in vivo*, producing effective synergistic chemotherapy, chemodynamic therapy, and photothermal therapy under the 808 nm laser irradiation. Together, the biomimetic nanoformulations showed a prolonged blood circulation and evasion of immune recognition *in vivo* to provide a bio-inspired strategy which may have the potential for the multi-synergistic therapy of breast cancer.

Graphical abstract



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Introduction

Breast cancer has emerged as a profoundly pernicious malignancy among women in contemporary times. (Kumbhar et al., 2022) Conventional therapeutic methods such as surgical resection, chemotherapy (CT), and radiation therapy (RT) may lead to substantial challenges, (Zhang et al., 2023) including elevated rates of tumor recurrence, impairment of normal cellular function, and the emergence of multidrug resistance, which make breast cancer patients endure significant and far-reaching adverse effects. (Wang et al., 2020, Wang et al., 2019) Therefore, to overcome the limitations of traditional therapies and improve breast cancer treatment, it is crucial to develop a novel nanomedicine delivery platform that enables the synergistic combination of multiple treatment modalities. (Chen et al., 2023, Huang et al., 2020) Fortunately, significant advances in nanotechnology have opened up new possibilities for the development of cancer therapies. (Wang et al., 2022).

Among these emerging nanotechnology-based therapeutic strategies, chemodynamic therapy (CDT) has attracted considerable attention due to its minimal side effects and tumor-specificity. (Jana et al., 2021, Shao et al., 2022) As a reactive oxygen species (ROS)-mediated reaction, CDT can facilitate the production of hydroxyl radicals from endogenous hydrogen peroxide through Fenton or Fenton-like reactions in the presence of metal ion catalysts (such as Fe, Cu, Mn, etc.), without relying on external light sources or stimuli. (Xu et al., 2022, Shi et al., 2020, Song et al., 2021) Moreover, photothermal therapy (PTT) represents remarkable therapeutic potential as an innovative method for treating tumors. (Ren et al., 2020, Zhang et al., 2021, Song et al., 2020) This localized thermotherapy induces cancer cell death and promotes the ablation of tumor tissue, while concurrently minimizing any potential damage to adjacent healthy tissue. (Cheng et al., 2021, Chen et al., 2021, Yang et al., 2020) Significantly, the local heat generated by the photothermal effect is beneficial to increase the permeability of tumor blood vessels and tumor cell membranes, (Fan et al., 2021, Khafaji et al., 2019) which can facilitate the absorption and accumulation of nanoparticles, ultimately augmenting multiple treatment modalities. Therefore, the combination of conventional chemotherapy with CDT/PTT therapy not only integrates the advantages of diverse treatment modalities to optimize the synergistic anti-tumor effect, but also mitigates the side effects. (Guan et al., 2022, Shi et al., 2022, Shi et al., 2023) This approach presents a promising strategy to improve therapeutic efficacy in tumor treatment.

However, the Fenton-like reaction catalyzed by Cu^{+} in CDT therapies exhibits superior kinetic and energetic properties compared to Fe^{2+} due to the low redox potential of Cu^{2+}/Cu^{+} (~0.16 V), (Xiao et al., 2021, Wang et al., 2022, Wang et al., 2022) which can

facilitate the efficient oxidation of Cu^{+} to Cu^{2+} in the weakly acidic tumor microenvironment. Simultaneously, due to the inherent toxicity of free metal ions to normal cells, (Ma et al., 2019) it is essential to explore materials with controlled release capabilities for incorporating metal ions, which can minimize damage to normal cells and enhance the efficacy of tumor treatment.

Metal organic framework materials (MOFs) have attracted significant attention from researchers due to their high porosity, large specific surface area, tunable pore size and biodegradability. (Di et al., 2023, Cheng et al., 2022, Rojas et al., 2019) Among them, zeolitic imidazolate framework-8 (ZIF-8), represents a typical class of MOF materials, exhibiting excellent biocompatibility and pH-responsive biodegradation, presenting considerable prospects for application in the biomedical field. (Li et al., 2022, Ding et al., 2023, Meng et al., 2022) However, due to the inadequate photothermal properties of the MOF, it is unable to efficiently kill cancer cells within a short period of time, and the reactive oxygen produced is insufficient for their eradication. Polydopamine (PDA) is a naturally occurring derivative of melanin in the human body that exerts excellent photothermal conversion efficiency. This phenomenon is attributed to the substantial presence of π electrons within PDA's molecular structure, (Li et al., 2021, Xu et al., 2023, Chu et al., 2023) and it can also be used to improve materials' photocatalytic properties through the fast charge carriers transportation. With these in mind, we hypothesise that modification of MOFs using PDA could enhance the photocatalytic activity and photothermal effect. This enhancement would be achieved through the acceleration of photogenerated electron transfer and heightened light absorption. However, the challenge of potential immune recognition that numerous nanoparticles encounter during delivery processes necessitates frequent surface modifications to prolong blood circulation time and improve drug accumulation at tumor sites. (Liu et al., 2019, Zhao et al., 2020) Recently, the cell membrane-coated nanoparticles (CMNPs) technology has been widely applied as a novel camouflage and modification strategy in cancer therapy. (Liu and Huang, 2022, Zeng et al., 2023, Oroojalian et al., 2021) Among them, erythrocyte membranes extracted from erythrocytes are often applied to wrap the outer surface of nanoparticles due to their excellent immune evasion abilities (Zheng and Xiao, 2022, Li et al., 2020) and prolonged blood circulation half-life characteristics, (Liu et al., 2022, Bao et al., 2021) which can effectively accumulate in tumor tissues through enhanced permeability and retention (EPR) effects, (Wu et al., 2023) providing a new way to achieve efficient drug utilization.

Herein, a multifunctional biomimetic composite nanomedicine based on metal–organic frameworks was designed for efficient synergistic CDT/CT/PTT therapy for the treatment of breast cancer. Briefly, Cu/ZIF-8 nanoparticles prepared by the ion-doping method could achieve a controlled release of copper ions in the tumor microenvironment to trigger effective CDT therapy without causing damage to normal cells due to the inherited pH-sensitive properties of ZIF-8 nanoparticles. A clinical anti-tumor drug, 10-hydroxycamptothecin (HCPT), was selected for loading into Cu/ZIF-8 to achieve combined CDT/CT therapy. To endow the composite nanoformulations (HCPT@Cu/ZIF) with excellent photothermal performance, a polydopamine (PDA) coating layer was introduced on the surface of HCPT@Cu/ZIF to form HCPT@Cu/ZIF@PDA composite nanoformulations. They could trigger PTT with the aid of near-infrared light irradiation, which simultaneously could facilitate the CDT therapy effect and promote effective drug release as well. Finally, the HCPT@Cu/ZIF@PDA composite nanoformulations would be camouflaged by wrapping of red blood cell membrane to achieve an enhanced EPR effect while improving immune evasion ability and prolonging blood circulation to promote aggregation at tumor sites.

Section snippets

Materials

Zinc nitrate hexahydrate ($Zn(NO_3)_2 \cdot 6H_2O$), cupric nitrate trihydrate ($Cu(NO_3)_2 \cdot 3H_2O$), 2-methylimidazole ($C_4H_6N_2$, 2-MIM), 10-hydroxycamptothecin (HCPT) and dopamine hydrochloride (DA·HCl) were purchased from Aladdin Bio-Chem Technology Co., Ltd (Shanghai, China). 2,7 dichlorodihydrofluorescein diacetate (DCFH-DA), calcein-AM/PI double stain kit, 4′,6-diamidino-2-phenylindole (DAPI), 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT), and JC-1 were purchased from Beyotime

Preparation and characterization of Rm-HCuZP nanoformulations

The preparation procedure of red blood cell membrane-coated functionalized Cu-doped metal organic framework nanoformulations (Rm-HCuZP) is shown in Scheme 1a. Firstly, Cu-doped ZIF-8 nanoparticles (CuZ) were synthesized by an ion-doping strategy using a modified method. (Chu et al., 2021, Xie et al., 2019) These CuZ nanoparticles have a rhombic dodecahedral structure with an average diameter of ~ 100 nm that is confirmed by TEM (Fig. 1a) and SEM (Figure S1) measurements. Fig. 1e shows the X-ray

Conclusions

In summary, a metal–organic framework-based bionic composite nanodrug (RBCM-HCPT@Cu/ZIF-8@PDA) is developed for synergistic treatment of breast cancer using CDT/CT/PTT therapy. Due to the surface coating of the erythrocyte membrane, Rm-HCuZP nanoformulations are endowed with the ability to prolong blood circulation, evade immune recognition, and enhance EPR effects, facilitating their aggregation at tumor sites. In addition, the acid-sensitive property of ZIF-8 realizes the effective release of

Author contributions

L. R. and J. Z. produced composite nanoformulation and performed cell and animal experiments; L. R., Y. S. and G. J. analyzed the results and wrote the draft of manuscript; Y. S. and G. J. conceived the idea and designed the experiments; L. N. and A. S. provided suggestions and commented on the manuscript; K. E. Y., U. E. A. and S. O. S. reviewed the manuscript.

CRediT authorship contribution statement

Luping Ren: Methodology, Investigation, Data curation, Conceptualization. **Yanfang Sun:** Supervision, Project administration, Methodology, Investigation. **Junhao Zhang:** Methodology, Investigation, Formal analysis, Data curation. **Lei Nie:** . **Amin Shavandi:** . **Khaydar E. Yunusov:** Writing – review & editing, Visualization, Validation. **Uladzislau E. Aharodnikau:** . **Sergey O. Solomevich:** . **Guohua Jiang:** Writing – original draft, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References (70)

- X.J. Chen *et al.*

  Photothermal/matrix metalloproteinase-2 dualresponsive gelatin nanoparticles for breast cancer treatment
  Acta Pharm. Sin. B
  (2021)
- Y. Cheng *et al.*

  Microwave-triggered/HSP-targeted gold nano-system for triple-negative breast cancer photothermal therapy
  Int. J. Pharm.
  (2021)
- H.Y. Chu *et al.*

  Biodegradable iron-doped ZIF-8 based nanotherapeutic system with synergistic chemodynamic/photothermal/chemo-therapy
  Colloids Surf. A Physicochem. Eng. Asp.
  (2021)
- X.J. Di *et al.*

  Tumor microenvironment-oriented MOFs for chemodynamic therapy
  Coord. Chem. Rev.
  (2023)
- X.N. Gao *et al.*

  A pH-responsive cascade nanoplatform with circulating oxygen supply for collaborative breast cancer treatment
  Chem. Commun.
  (2022)
- S.Q. Guan *et al.*

  A biodegradable ‘‘nano-donut” for magnetic resonance imaging and enhanced chemo/photothermal/chemodynamic therapy through responsive catalysis in tumor microenvironment
  J. Colloid Interface Sci.
  (2022)
- H.S. Hao *et al.*

Mesoporous calcium peroxide-ignited NO generation for amplifying photothermal immunotherapy of breast cancer
Chem. Eng. J.
(2022)

- Y. Huang *et al.*

Three birds with one stone: a ferric pyrophosphate based nanoagent for synergetic NIR-triggered photo/chemodynamic therapy with glutathione depletion
Chem. Eng. J.
(2020)

- L. Jia *et al.*

Ultrasound-enhanced precision tumor theranostics using cellmembrane-coated and pH-responsive nanoclusters assembled fromultrasmall iron oxide nanoparticles
Nano Today
(2021)

- P. Kumbhar *et al.*

Nanoparticulate drugs and vaccines: breakthroughs and bottlenecks of repurposing in breast cancer
J. Control. Release
(2022)